

BIOCHEMISTRY LEARNING MODULES

This page contains biochemistry learning modules. Each has a mini-quiz at the end to check your understanding of the content.

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Gluconeogenesis

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Glycogen storage diseases

Glycolysis

Hartnup disease and Fanconi syndrome

Hexose monophosphate (HMP) shunt

Homocystinuria

Krebs (TCA) cycle

Kwashiorkor vs Marasmus vs Cretinism

Lactase deficiency (lactose intolerance)

Lactulose vs Neomycin

Lysosomal storage diseases

Maple syrup urine disease

Marfan syndrome

Menkes syndrome

Mitochondrial disorders

Phenylketonuria (PKU)

Phakomatoses

Regulation of glycogen metabolism

Trinucleotide repeat (TNR) disorders

Urea cycle, Orotic aciduria, OTC deficiency

USMLE annoying lab techniques

Vitamin A, Zinc, Selenium

Vitamin B1 (Thiamine) + Wernicke-Korsakoff

Vitamins B2 (Riboflavin) + B3 (Niacin)

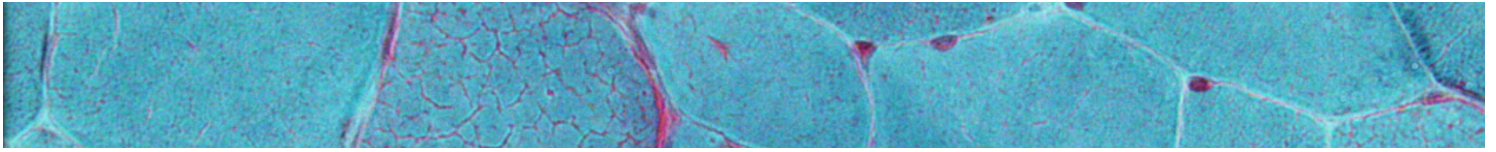
Vitamins B5, B6, and B7

Vitamins B9 (Folate) + B12

Vitamins C and E

Vitamin D for the USMLE

Vitamin K and Warfarin



BIOCHEMISTRY

α 1-antitrypsin deficiency

by MEHLMANMEDICAL

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Inheritance is HY

- Although **homozygous Z-alleles = disease**, the genetics are NOT autosomal recessive; the allelic expression is demonstrated in a **codominant** fashion.
- If they ask you about the inheritance of α 1-antitrypsin deficiency, **the answer is codominant inheritance**. NOT autosomal recessive.
- AB RBC antigens are also codominant.

USMLE wants you to know what α 1-antitrypsin normally does

- α 1-antitrypsin is **produced in the LIVER**. α 1-antitrypsin deficiency is notably known to cause emphysema, but the enzyme is **NOT** produced in the lungs; it is produced in the liver.
- It breaks down **elastase**. This is really important. In other words, it is not trypsin that builds up (paradoxically); it is **elastase** that does.
- The misfolded α 1-antitrypsin protein **never reaches the lungs**; it is sequestered in the liver.

Disease presentation

- Causes **hepatic cirrhosis** generally by middle-age. Patients who drink alcohol have $\uparrow\uparrow$ risk of liver disease.
- α 1-antitrypsin deficiency causes **pan**-acinar (or **pan**-lobular) emphysema – i.e., the entire respiratory zone of the lung, proximal to distal, is affected.
- In contrast, smoking classically causes **centri**-acinar (or **centri**-lobular) emphysema, where the more proximal respiratory zone is affected first.
- USMLE will tell you there are bullous changes on CXR, increased anterior-posterior diameter, and/or lucency of lung fields **in someone who is relatively young and a non-smoker**.
- Frequent question stem is young non-smoker with emphysema who's father died from alcoholic cirrhosis and who's brother has similar Sx.

Smoking increases the risk of emphysema in diseased patients. Yes, that's obvious, but the USMLE wants you to know this is *because* smoking **also increases elastase activity**.

The combination of $\downarrow$ elastase breakdown 2° to α 1-antitrypsin deficiency + $\uparrow$ elastase activity from smoking = faster onset of emphysema.

However the emphysema in an α 1-antitrypsin deficiency question is always **pan-acinar**, even if they also mention the patient is a smoker.

Cellular-level points

- Liver biopsy in a patient with α 1-antitrypsin deficiency reveals intracellular **PAS-positive aggregates**. The USMLE really likes that for some reason, so know it. The aggregates are **misfolded glycoprotein**.
- The cirrhosis in advanced disease is due to the accumulation of the misfolded protein leading to hepatocyte death, whereas in the lungs, it is the $\uparrow$ elastase that causes the emphysema.
- The misfolded α 1-AT protein accumulates in the **endoplasmic reticulum** of hepatocytes. This is the same as with **cystic fibrosis**, where the misfolded CFTR channel accumulates in the RER of cells and is not delivered to the cell surface.

—

1. Inheritance pattern of α 1-antitrypsin deficiency?

- ☐ AR
- ☐ XR
- ☐ XD
- ☐ Codominant
- ☐ AD sometimes; codominant sometimes
- ☐ AD

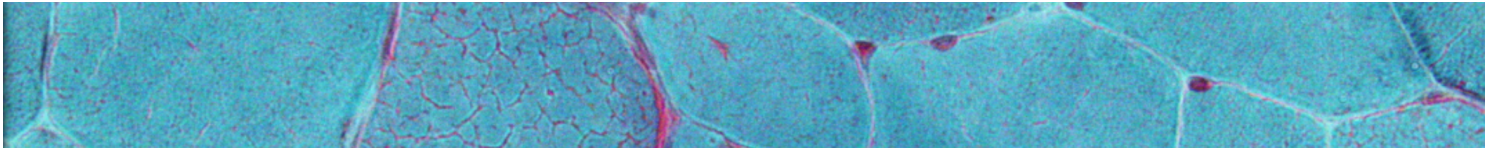
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HY USMLE Q #940 – Biochemistry

January 1, 2024



BIOCHEMISTRY

Abetalipoproteinemia and HY factoid about spur cells

by MEHLMANMEDICAL

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Abetalipoproteinemia is a condition where ApoB-48 and ApoB-100 production is deficient.

All you need to know about ApoB-48 is that it is the apolipoprotein responsible for allowing [chylomicrons](#) that are absorbed by the gut to be released into the circulation.

Fat droplets in bowel wall on biopsy = abetalipoproteinemia. Weird/unusual detail that sounds extraneous and low-yield, but there's a question floating around somewhere that shows large, clear droplets within enterocytes on biopsy, and the answer is abetalipoproteinemia.

The other important point about abetalipoproteinemia is that it leads to **acanthocytes (spur cells)**. These are spiky-looking RBCs. **If they show you a blood smear of spiky RBCs and mention intestinal/absorptive problems in the vignette, the answer is abetalipoproteinemia.**

Spur cells are the USMLE giveaway for abetalipoproteinemia.

Now for the greater value of this post (because many people reading this might already be aware of the association between abetalipoproteinemia and spur cells):

Acanthocytes are also seen in liver failure. Memorize that.

There's a USMLE question that mentions an elderly woman found unconscious in her home on a hot summer day with hyperthermia. They say she has acanthocytes on blood smear and ask for the diagnosis. The answer is liver failure.

Heat stroke = end-organ damage secondary to increased body temperature.

Heat exhaustion = no end-organ damage and less severe than heat stroke.

If you reason that the old lady has heat stroke, then that explains why she has acanthocytes in her blood. It's because she has end-organ failure (in this case, hepatic).

That's it. Would you rather read a superfluous, 3000-word essay that doesn't tell you exactly what you need to know.

—

1. What kind of biopsy specimen is seen in abetalipoproteinemia?

- ☐ Enterocyte; betalipoprotein aggregates
- ☐ Enterocyte; fat droplets
- ☐ Colonocyte; betalipoprotein aggregates
- ☐ Colonocyte; fat droplets

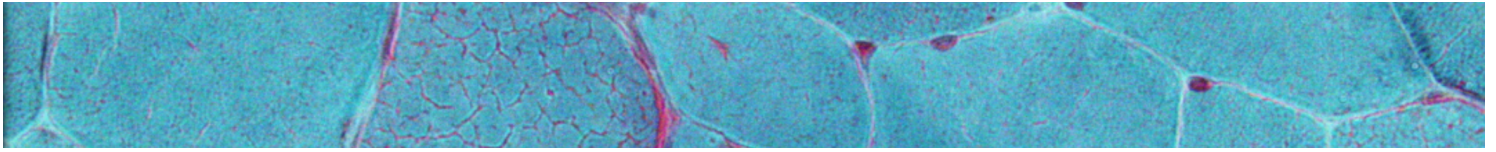
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Aldose reductase + Sorbitol + Galactitol

by MEHLMANMEDICAL

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A post for sorbitol + galactitol? What the fuck? Yeah, I know. A bit odd. But it's up to you whether you want to know the HY points or not.

High plasma glucose levels (i.e., in diabetes mellitus) = high intracellular sorbitol levels.

This is because **aldose reductase** is an intracellular enzyme that converts glucose to sorbitol.

Sorbitol can then cause osmotic injury to cells because it leads to greater intracellular retention of water relative to glucose, thereby causing cellular swelling.

If a USMLE question asks you *how* cataracts or neuropathy occurs in diabetes, **osmotic injury to cells** is the answer.

In contrast, the nephropathy, retinopathy, and atherosclerosis seen in diabetes are due to **non-enzymatic glycosylation of endothelial cells** by glucose, which leads to direct cellular damage.

Non-enzymatic glycosylation of endothelial cells = endothelial damage + ↑ permeability → atherosclerosis, diabetic nephropathy, retinopathy

Sorbitol accumulation in cells due to aldose reductase → cellular swelling / osmotic damage → cataracts, neuropathy

—
All you need to know about **galactitol** is:

Galactose, via **aldose reductase**, → galactitol.

Aldose reductase converts:

Glucose → sorbitol

Galactose → galactitol

So who the fuck cares? It's because **the cataracts in galactose disorders are due to galactitol, not sorbitol.**

So the USMLE will tell you there's an infant with cataracts + reducing sugars in the urine (galactokinase deficiency), or cataracts + hepatomegaly + jaundice (classic galactosemia), and then they'll ask which enzyme is responsible for the cataracts, and you simply select **aldose reductase**.

And of course if they ask for the product of the reaction, you just select galactitol, not sorbitol.

Nothing dramatic. Short post. But HY information nevertheless.

—

1. Which of the following occur(s) due to non-enzymatic glycosylation of endothelial cells? (Select all that apply)

- ☐ Neuropathy
- ☐ Nephropathy
- ☐ Atherosclerosis
- ☐ Cataracts
- ☐ Retinopathy

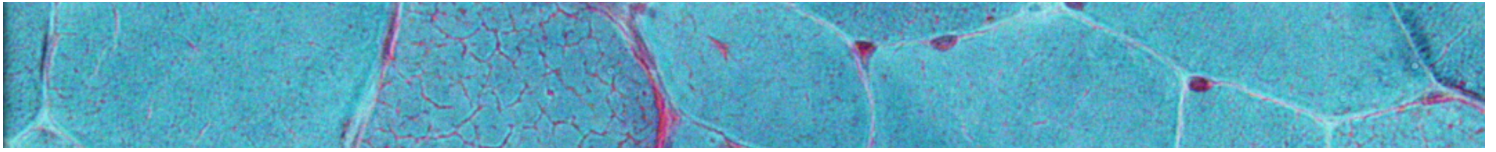
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BIOCHEMISTRY

Alkaptonuria

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For some magical reason, this is a USMLE favorite.

It is caused by a deficiency of **homogentisic acid oxidase** (homogentisate oxidase), which is an enzyme necessary for the breakdown of tyrosine to fumarate.

The highest yield thing you need to know is that the **urine becomes dark/black upon standing**, or with the addition of citrate. They will mention this in probably ~80% of alkaptonuria questions.

However ~20% of the time, they won't mention that the urine turns dark. **They'll instead say that the patient has athralgias (painful joints), where biopsy shows blue/black/brown connective tissue (ochronosis).** Homogentisate buildup in joints is toxic, which is why it causes discoloration and pain (ochronotic arthropathy). Rarely you might see a question that mentions brownish discoloration of the sclera.

Dude with urine that turns black on standing. This is caused by a defect in breakdown of which amino acid? **Tyrosine**

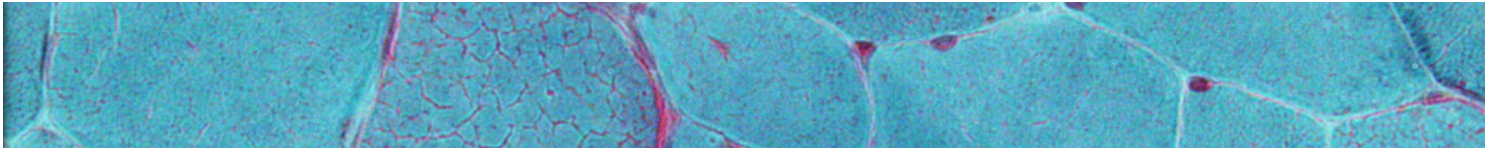
Dude has joint pain and blue/grey discoloration of the pinna of his ear and sclerae. Which enzyme is deficient? **Homogentisic acid oxidase**

That's all you need to know about alkaptonuria.

—

1. What is the enzyme deficiency in alkaptonuria?

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Angelman vs Prader-Willi syndromes

by MEHLMANMEDICAL

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These two conditions have tremendous importance on Step1 because of their genetics.

They arise either due to imprinting or uniparental disomy.

- **Imprinting** means receiving one allele from each parent but **one is preferentially silenced**.
 - **Maternal imprinting** means mom's allele is silenced; only dad's allele is expressed.
 - **Paternal imprinting** means dad's allele is silenced; only mom's allele is expressed.
 - For many genes, *it is normal* that although two copies are received (one from each parent), only one copy may be expressed due to the other being preferentially silenced (via methylation).
 - This is one of the reasons why two individuals of the same gender cannot produce an offspring through *in vitro* techniques, even if the combination of chromosomes is balanced.
- **Uniparental disomy** means both of an individual's alleles for a gene are received from the same parent (i.e., instead of getting one from each parent).
 - **Maternal uniparental disomy** means receiving both alleles from mom.
 - **Paternal uniparental disomy** means receiving both alleles from dad.
 - **Uniparental heterodisomy** means getting one copy of each of the parent's alleles (i.e., one from each chromosome).
 - **Uniparental isodisomy** means getting two copies of the same allele from the same parent (i.e., from the same chromosome).
 - (I talk about in [this article](#) a HY point about how this relates to CF).

Prader-Willi syndrome (PWS)

- Many associated genes on **chromosome 15**
- Classically presents as an **obese patient with mental impairment and hyperphagia**.
- Due to either **maternal imprinting** or **maternal uniparental disomy**.

Maternal imprinting in PWS

- Accounts for majority of PWS cases
- **Maternal imprinting** (gene received from mom is silenced) + **paternal gene deletion/mutation**
- This means the mom's gene is received and silenced (as normal), but dad's defective gene is responsible for the disease.
- In other words, in order to *not* get Prader-Willi syndrome, the allele received from dad must be normal. Mom's allele can by all means be mutated, but it doesn't matter because it's silenced.
- **"Willi hates his dad"** because dad's gene is deleted/mutated.

Maternal uniparental disomy in PWS

- Accounts for minority of PWS cases
- Both alleles are received by mom, and both are silenced.
- Even if they are completely normal / non-mutated, because they're both silenced, the child does not have any expressed allele and therefore has the disease (i.e., it's as though he has two deleted or mutated copies).

Angelman syndrome (AS)

- *UBE3A* gene on **chromosome 15**
- Due to either **paternal imprinting** or **paternal uniparental disomy**.
- Classically presents as a patient with **mental impairment** who **laughs a lot and/or is easily made happy** ("happy puppet")

Paternal imprinting in AS

- Accounts for majority of AS cases
- **Paternal imprinting** (gene received from dad is silenced) + **maternal gene deletion/mutation**
- This means the dad's gene is received and silenced (as normal), but mom's defective gene is responsible for the disease.
- In other words, in order to *not* get Angelman syndrome, the allele received from mom must be normal. Dad's allele can by all means be mutated, but it doesn't matter because it's silenced.
- **"Mom is not an angel"** because **mom's gene is deleted/mutated**.

Paternal uniparental disomy in AS

- Accounts for minority of AS cases
- Both alleles are received by dad, and both are silenced.
- Even if they are completely normal / non-mutated, because they're both silenced, the child does not have any expressed allele and therefore has the disease (i.e., it's as though he has two deleted or mutated copies).

Prader-Willi syndrome = **maternal imprinting** or **maternal UPD**

Angelman syndrome = **paternal imprinting** or **paternal UPD**

Both conditions are on **chromosome 15** but are *not* reciprocal imprints/UPDs of the same gene.

Angelman is usually *UBE3A*. PWS has many associated genes.

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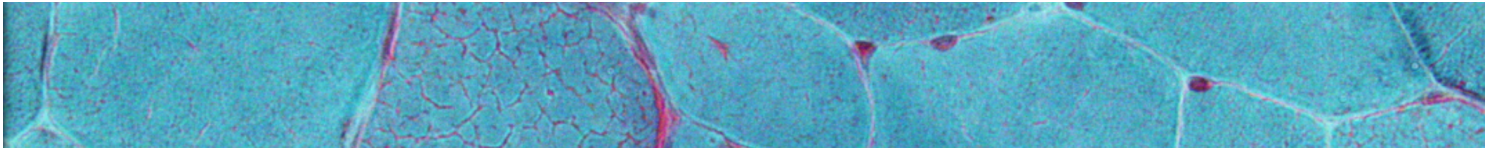
1. What is maternal vs paternal imprinting?

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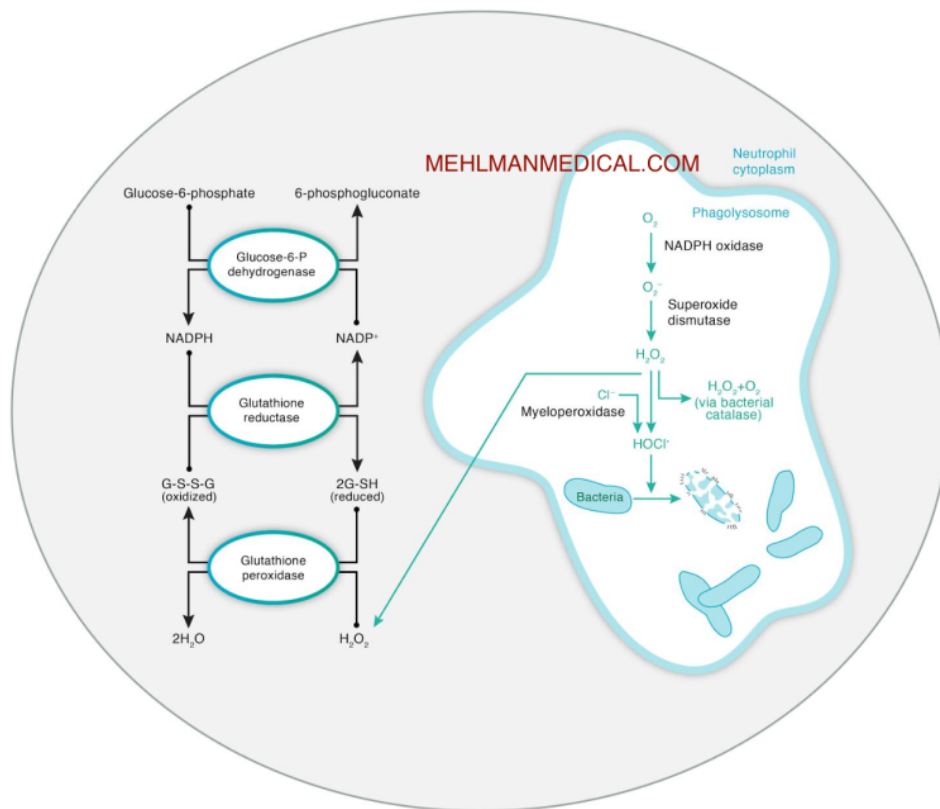
Chronic granulomatous disease (NADPH oxidase deficiency)

by MEHLMANMEDICAL

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In order to discuss chronic granulomatous disease (NADPH oxidase deficiency), we need to introduce a process known as “respiratory burst,” which is a series of reactions through which phagocytes – most notably neutrophils – create reactive oxygen intermediates (ROI) to kill invading microbes.

NADPH oxidase is the critical enzyme in this system (probably because it’s the most upstream in the reaction pathway).

For whatever magical reason, the USMLE likes to ask the substrate for this enzyme, and the answer is **molecular oxygen**.

People easily memorize NADPH oxidase deficiency for their boards, but then when they're asked, "Ok, but what's the enzyme act on? In other words, what's the substrate of the enzyme?" They're like, "Uhh..yeah.."

So once again, what is the substrate for NADPH oxidase? **Molecular oxygen**. Crazyiness.

As you can see, the respiratory burst ultimately leads to H_2O_2 and bleach (HOCl^-) production, which kill microbes.

H_2O_2 that is not converted into bleach exits the phagocyte and is neutralized to H_2O by catalase and glutathione peroxidase. **Reduced glutathione** and **NADPH** are what allow this neutralization to occur.

Reduced glutathione has an $-\text{SH}$ group. $-\text{SH}$ groups, NADPH, and NADH = reducing agents on the USMLE

In contrast, oxidized glutathione has a disulfide bond ($-\text{S}-\text{S}-$). $-\text{S}-\text{S}-$, NADP^+ , and NAD^+ = oxidizing agents on the USMLE

Tangential but HY: N-acetylcysteine (for acetaminophen toxicity) and Mesna (for cyclophosphamide toxicity) also both have $-\text{SH}$ groups.

The NADPH used for the respiratory burst is produced from the hexose monophosphate shunt (HMP shunt) via **glucose-6-phosphate dehydrogenase**.

This is why patients with G6PD deficiency are susceptible to oxidizing drugs (e.g., dapsone, primaquine) and hemolytic anemia, because their NADPH production is less efficient, so they can't neutralize H_2O_2 and other oxidizing agents as readily, leaving their RBC membranes more prone to lysis.

Now we can introduce the crux of why the respiratory burst is important for the USMLE:

Chronic granulomatous disease (CGD)

Chronic granulomatous disease = NADPH oxidase deficiency

This disease is characterized by **increased susceptibility to catalase-positive organisms**. Catalase is the enzyme that breaks down H_2O_2 .

Humans **without** CGD: Production of H_2O_2 via respiratory burst is $\gg \gg$ catalase produced by organisms $\rightarrow$ organisms are overwhelmed + die

Human **with** CGD: Production of H_2O_2 via respiratory burst is $<$ catalase produced by organisms $\rightarrow$ organisms can tolerate phagocyte environment + survive

Organisms that produce catalase are able to neutralize *small amounts* of H_2O_2 , but not large amounts. So in a typical person who does *not* have NADPH oxidase deficiency, the amount of hydrogen peroxide he or she produces far exceeds what catalase (+) organisms can handle, so therefore there's no innate susceptibility to these organisms.

A general mnemonic for catalase-positive organisms is **C SHAPES**:

Candida, Serratia, H. pylori, Actinomyces, Pseudomonas, E. coli, S. aureus

You'll either get a vignette that is overwhelmingly CGD based on Serratia, Candida, and/or E. coli showing up in a child, OR

The vignette will mention a fairly non-specific Hx of mere Staph infections, but you'll easily be able to eliminate the other answer choices to choose CGD anyway – i.e., "Ok, well this is clearly not SCID, or Leukocyte-adhesion deficiency, or Chediak-Higashi syndrome, etc." And you just eliminate to get there.

Rarely, questions might throw in supporting details like **mouth ulcers**, since up to 50% of patients with CGD have Crohn-like symptoms.

CGD patients frequently have:

- **Aphthous ulcers (mouth ulcers)**

- Urogenital tract obstruction due to granulomas
- 50% have Crohn-like symptoms (bleeding per rectum / malabsorption)

But in general, merely knowing the catalase (+) organisms is sufficient.

Neutropenia on Step1 frequently presents as **mouth ulcers**. Notice that in CGD, although there isn't neutropenia, neutrophil function is impaired.

USMLE questions also might rarely mention **lymph nodes with "leaking purulent material"** as synonymous with CGD.

Diagnosis is made via a positive **dihydrorhodamine test**.

Nitroblue-tetrazolium test is now obsolete and the wrong answer.

If they give both as answer choices, **choose dihydrorhodamine test**.

USMLE-favorite treatment for CGD is **IFN-γ**.

Myeloperoxidase

As you can see from the respiratory burst image, myeloperoxidase is a phagocytic enzyme that converts hydrogen peroxide into bleach.

If they ask you which enzyme is the *second most* effective bactericidal mechanism in phagocytes, **the answer is myeloperoxidase**. If they list NADPH oxidase, the reason that's wrong is because that's the *most effective*.

But the USMLE actually doesn't care so much about myeloperoxidase deficiency. If you were to be asked that on your actual exam, that would in fact be quite low-yield. The question writers are more interested in seeing if you know how the enzyme relates to acute myelogenous leukemia (AML).

Auer rods are most often seen on blood smear in the M3 subtype of AML, aka acute promyelocytic leukemia (APL). If they ask you what Auer rods are composed of, **the answer is myeloperoxidase**.

The release of myeloperoxidase into the blood during the Tx of leukemia can lead to **disseminated intravascular coagulation (DIC)**.

Because myeloperoxidase composes Auer rods, it should be articulated that it is a heme-containing pigment with a blue-green color. Why is this important?

Because it is myeloperoxidase that primarily gives sputum its color. **NOT** shed epithelial cells, leukocytes, or dead bacteria.

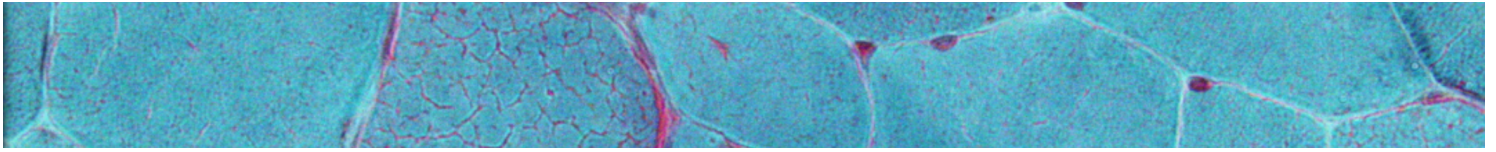
1. What is the substrate for NADPH oxidase?

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Collagen I, Osteogenesis imperfecta, Osteopetrosis

by MEHLMANMEDICAL

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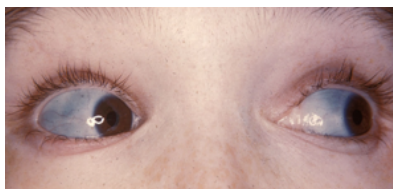
Collagen I

- Found in **skin and bone**
- Important for **late**-wound repair
- In other words, after skin injury, the initial pink, granulation tissue has ↑ type III collagen and ↓ type I, but as the skin ↑ in strength and heals, the type III collagen is replaced by type I collagen. Therefore, **type I collagen has ↑ strength**.
- Osteoid (unmineralized bone) **secreted by osteoblasts** is primarily type I collagen
- The USMLE occasionally tests that type I is found in **dentin** and **cornea**.

Osteogenesis imperfecta (OI; "brittle bone disease")

- Usually caused by deficiency of type I collagen (COL1A# genes).
- Inheritance varies depending on type of OI, but is usually AD.
- There are 17+ types of OI, with many different genes involved.
- **USMLE likes defective hydrogen bonding as an answer for OI.**

Highest yield features



Blue sclerae

- Most of the time vignettes won't mention blue sclerae because it's too easy / buzzwordy, even though it's the highest yield feature.

Conductive hearing loss

- **Conductive** hearing loss seen in osteogenesis imperfecta is due to malformation of the middle ear bones (ossicles)

Child abuse only = **avoids eye contact upon being spoken to**, spiral fractures, posterior rib fractures, retinal hemorrhages / detachment, subdural hematoma, circular burns, burns that spare flexor creases

Osteogenesis imperfecta = **doesn't respond upon being spoken to**, blue sclerae, abnormal dentition

Fractures at different stages of healing

- Child abuse and osteogenesis imperfecta can **both** present with multiple fractures in the USMLE question.

A mother brings her child in with fractures at different stages of healing. The physician notes that the child avoids eye contact when spoken to.

Answer = child abuse, or “**contact social services**.” On Step1, avoidant behavior = child abuse.

A mother brings her child in with fractures at different stages of healing. The physician notes that the child does not respond when spoken to.

Answer = osteogenesis imperfecta, or “**educate parent about child's condition**.” On Step1, non-response to physician = deafness, not avoidant behavior.

Genetics point

- With the most common type (type I OI) due to ↓ production of type I collagen, this is called the **null allele effect**, where disease occurs because there simply is not enough type I collagen.
- In other words, the normal collagen yielded by **the normal gene copy is not affected by the mutant allele**.
- This is in contrast to types II and III OI, for instance, which yield an abnormal type I collagen that **physically impairs the function of** the healthy collagen produced by the normal allele. This is called a **dominant-negative effect**, and frequently leads to more severe disease **and/or miscarriage**.

If the question gives you a classic presentation of a **child with multiple fractures and blue sclerae** and then asks for the mechanism of disease, **the answer is null allele effect** (type I).

However, if the question tells you there's a woman with **repeated miscarriages** who finally gives birth to a child who demonstrates evidence of fractures *in utero*, **the answer is dominant-negative effect** (type II or III).

Osteopetrosis (Albers-Schönberg disease)



- Fracture disorder in children often mistaken for OI or child abuse
- Characterized by ↑ bone density due to ↓ osteoclast activity
- ↓ osteoclast activity due to deficiency of carbonic anhydrase II inside bone
- Carbonic anhydrase II normally yields an acidic interface via which osteoclasts can resorb bone
- If you subjectively rule out OI and child abuse in a question, think osteopetrosis as the answer.
- Calcium, phosphate, ALP, and PTH level **are all normal** in osteopetrosis (just as they are in osteoporosis).

- ☐ Bone
- ☐ Skin
- ☐ Dentin
- ☐ Cornea
- ☐ Early wound repair
- ☐ Late wound repair

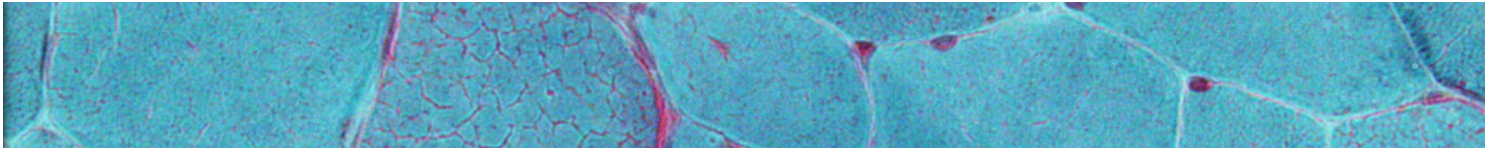
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January 1, 2024



BIOCHEMISTRY

Collagen II & III, Ehlers-Danlos syndrome

by MEHLMANMEDICAL

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Type II collagen

- Notably found in **cartilage**, **nucleus pulposus**, and **vitreous body**
- Sometimes **cleft palate** can also occur 2° to type II collagen mutations

Stickler syndrome

- Approximately 75% of **Stickler syndrome** cases are due to mutations in *COL2A1*.
- **Most important feature is deafness.**
- Since type II collagen is an essential component of vitreous body, these patients also frequently have **ocular problems**.

Type III collagen

- Found in **granulation tissue** (early wound healing)
- Also in **blood vessels**, uterus, and fetal tissue

Collagen III is the main component of reticulin

- Reticular cells secrete **reticulin**, a connective tissue protein composed of **type III collagen**
- Found predominantly in liver and bone marrow

Although **keloid scars** have ↑↑ production of both types I and III collagen, questions occasionally assess **keloid scars** = ↑ **type III collagen**.

Ehlers-Danlos syndrome (EDS)

- 13 different types of EDS, with many different genes and mutations involved
- Can be caused by defects in several different types of collagen, but on the USMLE Step1, the answer is **type III collagen**.
- **Hyperextensible skin**, **joint hypermobility**, and **joint subluxations** are common in EDS.



- ↑ risk of aortic aneurysm + rupture
- **Mitral valve prolapse** and **aortic regurgitation** are the two murmurs you should think about if you get a stethoscope question.
- ↑ risk of **circle of Willis berry (saccular) aneurysms, leading to subarachnoid hemorrhage (exceedingly HY)**

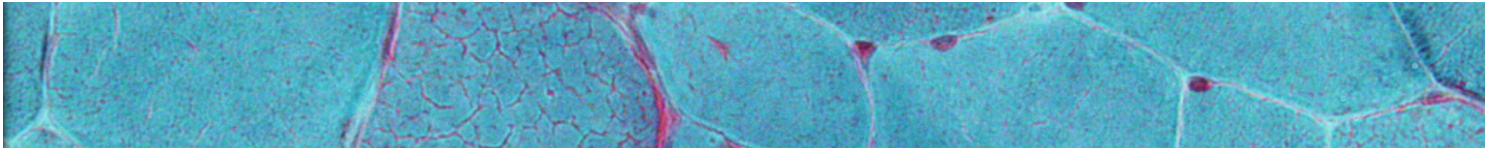
—

1. Where is collagen II found in abundance? (Select all that apply)

- ☐ Reticulin
- ☐ Nucleus pulposus
- ☐ Bone
- ☐ Uterus
- ☐ Early wound healing
- ☐ Late wound healing
- ☐ Vitreous body
- ☐ Cartilage

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BIOCHEMISTRY

Collagen IV, Alport & Goodpasture syndromes

by MEHLMANMEDICAL

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Type IV collagen

- Found notably in **basement membranes, basal lamina**, and in the **lens of the eye**.
- **Laminin** is a major component of basal lamina. Therefore, laminin binds type IV collagen.

Alport syndrome

- *Mutations in type IV collagen genes (COL4A#)*
- **X-linked (HY on the USMLE)**
- Some sources say XR. Others say XD. The USMLE will never make you choose between XR and XD for Alport. But just know that it could theoretically be either.
- **Presents as ear and/or eye problems in a male with red urine** (i.e., neurosensory hearing loss, lens dislocations, hematuria)

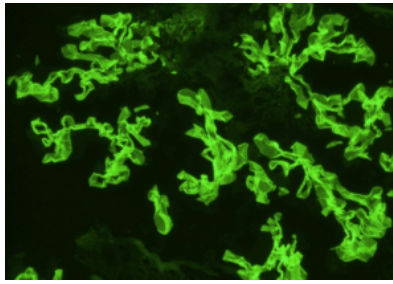
Goodpasture syndrome

- Autoantibodies *against* type IV collagen (i.e., anti-glomerular basement membrane Abs; **anti-GBM Abs**)
- More specifically, **type-II hypersensitivity due to autoantibodies against the alpha-3 chains of type-IV collagen** (2, 3, 4 = type-II hypersensitivity, alpha-3 chains, type-IV collagen).
- **A way to remember this is: "2, 3, 4! 2, 3, 4! 2, 3, 4! The Goodpasture is marching in the field. 2, 3, 4!"**

Alport syndrome = *mutations in type IV collagen*

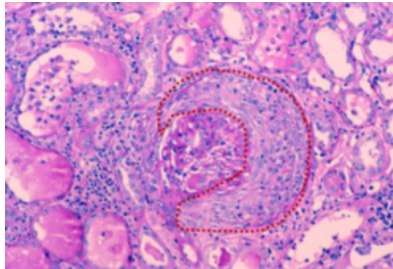
Goodpasture syndrome = *autoantibodies against type IV collagen*

- **Hemoptysis + hematuria** generally in a male in his 40s
- **Linear immunofluorescence** on biopsy of the skin, kidney, and lung because of the linear uniformity of basement membranes containing type IV collagen.



Linear immunofluorescence in Goodpasture syndrome. An image like this is HY on the USMLE.

- Is a cause of **rapidly progressive glomerulonephritis**, which will reveal **fibrin crescents** on renal biopsy under light microscopy.



Fibrin crescent under LM in RPGN.

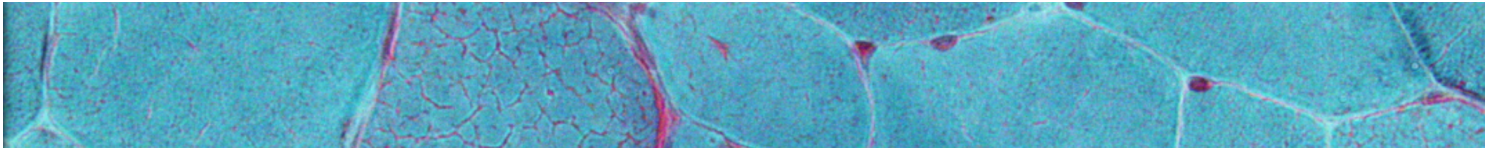
—

1. Where is collagen IV found in abundance? (Select all that apply)

- ☐ Basement membrane / basal lamina
- ☐ Lens of the eye
- ☐ Laminin
- ☐ Cartilage
- ☐ Alveoli
- ☐ Glomerulus

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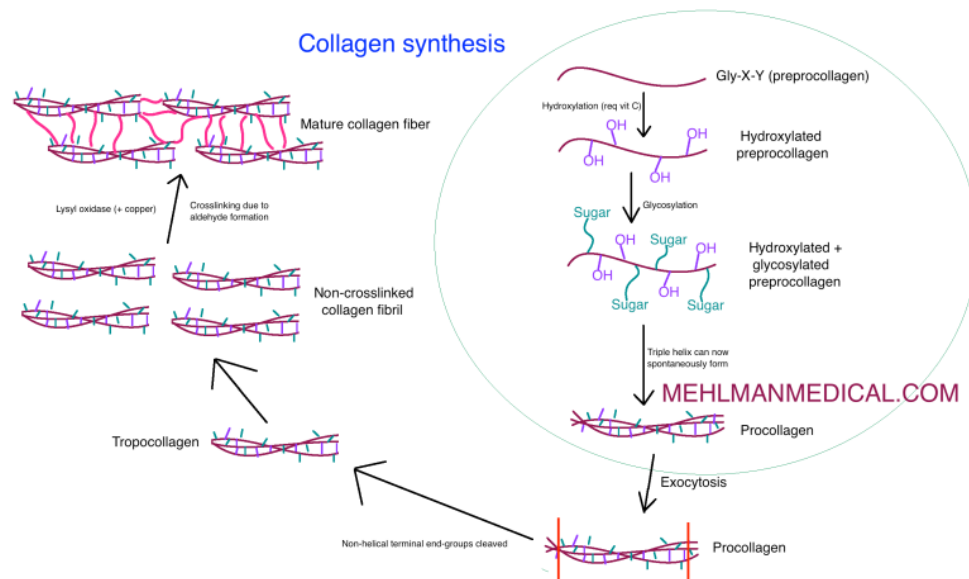
Collagen synthesis

by MEHLMANMEDICAL

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Collagen has a Glycine-X-Y primary structure

- Called **preprocollagen**
- Primary structure is a repeating sequence of **Gly-X-Y**, where X and Y can refer to proline, hydroxyproline or hydroxylysine.
- Glycine is the most abundant amino acid in collagen because it is reliably 1/3 of the primary structure.
- This also means if they ask you which amino acid is most reflective of collagen content of a tissue, **the answer is glycine**.
- The mere translation of glycine-X-Y repeats occurs at the **rough endoplasmic reticulum**.

Hydroxylation occurs next

- Creates hydroxylated preprocollagen
- Increases hydrogen bonding between primary Gly-X-Y polypeptides
- Requires vitamin C as a cofactor
- Contributes to secondary structure (H-bonding)
- **Osteogenesis imperfecta (↓ collagen I) leads to defective hydrogen bonding**

Then glycosylation

- Creates glycosylated + hydroxylated procollagen
- Strengthens bonding between polypeptides
- Contributes to tertiary structure
- More disulfide bonds form between polypeptides

Triple helix can now spontaneously form

- Procollagen now bears the adequate thermodynamics to spontaneously spin into a triple helix.
- This triple helical form is now called **procollagen**.

Procollagen is then exocytosed from the cell

- In the extracellular space, the procollagen has **disulfide-rich non-helical end-groups** that require cleavage.

Non-helical end-groups are cleaved from procollagen

- **Procollagen peptidase** (aka propeptidase) then proteolytically cleaves off these terminal regions, thereby decreasing the procollagen's solubility in water ~1000-fold.
- If these regions are not cleaved off, ↑ H₂O solubility weakens collagen.
- Once these N- and C-terminal non-helical regions are cleaved off, the procollagen is now called **tropocollagen**.
- [Ehlers-Danlos syndrome](#) (usually ↓ collagen III) can also be caused by deficiency of procollagen peptidase.

Tropocollagen then arranges into closely packed collagen fibrils

- Tropocollagen molecules then align to form **collagen fibrils**

Collagen fibrils are then crosslinked to become mature collagen fibers

- Collagen fibrils are crosslinked via **lysyl oxidase** to make **mature collagen**.
- Lysyl oxidase is a **copper-dependent enzyme**.
- Lysyl oxidase creates aldehydes from the -OH groups. The aldehydes can then crosslink.
- [Menkes syndrome](#) leads to ↓ activity of lysyl oxidase because of copper deficiency.
- (The Menkes syndrome post is [here](#)).

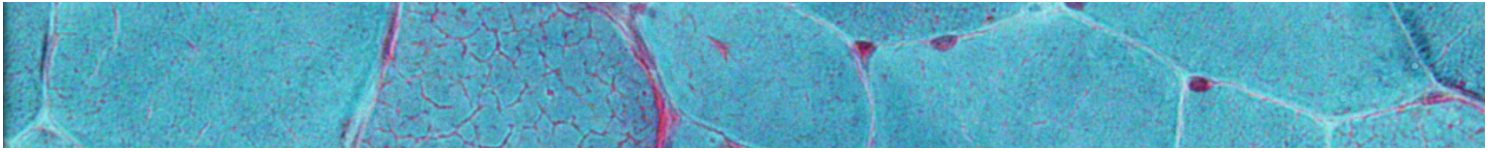
Loss of aesthetics 2° to aging (wrinkles) is caused by ↓ collagen fibril production. All collagen end-products ↓ with aging. **Crosslinking is unaffected.**

—

1. What's the most abundant amino acid in collagen?

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BIOCHEMISTRY

Cystinuria

by MEHLMANMEDICAL

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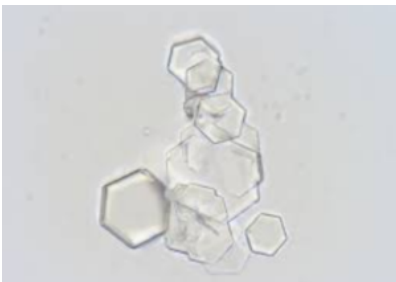
Cystine = 2 cysteine molecules bound together by a disulfide bond.

Each cysteine has an -SH (thiol group), and oxidation makes them join together to form -S-S-. The same goes for homocysteine, where two homocysteines join to form homocystine.

In cystinuria, the PCT of the kidney cannot reabsorb cysteine, so the buildup of cysteine leads to the formation of **hexagonal** cystine stones in the renal tubules.

If the patient is young, there is likely an underlying hereditary pathology, so **cystine stones** should be high on your differential.

A USMLE favorite is showing you a picture of **hexagonal** crystals in the urine. The diagnosis is cystinuria.



The reabsorption of cysteine is not isolated. It is part of a larger malabsorptive pathology characterized by an inability to absorb **cysteine, ornithine, lysine and arginine (COLA)**.

Therefore, on Step1, inability to absorb cysteine = inability to absorb ornithine, lysine and arginine.

If a patient with Hx of cystinuria develops calcium phosphate stones and they ask you why, it's because the **citrate** or HCO_3^- used as Tx increased the pH of the urine enough to allow for $\text{Ca}_3(\text{PO}_4)_2$ stone formation. **Furosemide** is a wrong answer. Although loops cause hypercalciuria, they aren't Tx for cystinuria.

For cystinuria, either a picture of the hexagonal stone or a mention of it will be made ~50% of the time.

About ~15% of the time, it will rely on your knowing the COLA association.

Another ~15% of the time they will give a relatively vague vignette of non-specific nephrolithiasis in an otherwise healthy patient in his or her late-teens or 20s.

~20% of the time they'll mention in a vignette that the patient has a (+) **nitroprusside cyanide test**, or they'll say that the **urine becomes purple/blue/magenta** when nitroprusside and cyanide are added. This is a diagnostic test for both cystinuria and homocystinuria. The -S-S- becomes 2x -SH when reacted with cyanide, and then nitroprusside reacts with -SH to induce a color change.

If they mention cystine stones, they want you to know that alkalinizing the urine helps dissolve them. **Citrate** is commonly the answer when they ask for the treatment. **Penicillamine** rarely also shows up as an answer (helps cleave the -S-S- in cystine).

Penicillamine is used as copper chelation therapy in Wilson disease. It also causes **drug-induced SLE w/ (+) anti-histone Abs**. For drug-induced SLE, remember Mom is **HIPP**: Minocycline, Hydralazine, INH, Procainamide, Penicillamine

—

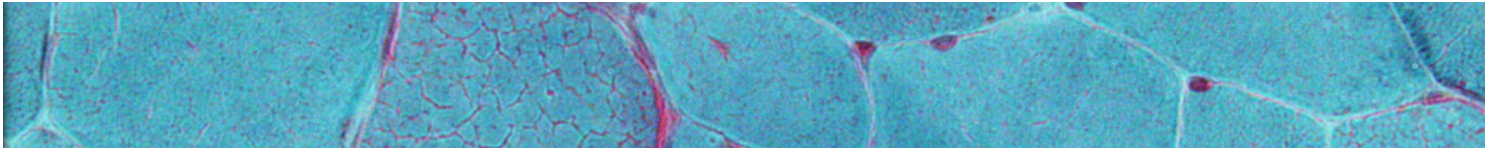
1. Cystine stones have which shape?

- ☐ Hexagonal
- ☐ Rhomboid
- ☐ Needle
- ☐ Coffin-lid

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BIOCHEMISTRY

Cystic Fibrosis vs Kartagener syndrome

by MEHLMANMEDICAL

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Cystic fibrosis (CF)

Cystic fibrosis likely wins the award for most frequently tested condition on USMLE Step1. Know all of the information printed in this entry regarding this disease. In fact, this entry is probably worth an actual five points on your Step 1.

Inheritance

- Autosomal recessive
- Chromosome 7
- Classically caused by a **deletion ($\Delta F508$; deletion of phenylalanine)** in the **CFTR** gene, which normally codes for **CFTR protein** (cystic fibrosis transmembrane regulator). There are **many** potential mutations; this is merely just the most HY.
- CF is the most common genetic disease leading to ↓ lifespan in the Caucasian population.

How to break a 260 on Step 1:

CFTR is a cAMP-regulated and ATP-gated chloride channel.

cAMP activates protein kinase A, which catalyzes the ATP hydrolysis.

CFTR has twelve transmembrane components; two domains, each with six segments (completely outrageous and ridiculous).

How the disease works (this mechanism is really really HY!)

- CFTR is a transmembrane **chloride channel** that normally **absorbs Cl^- in sweat but secretes it everywhere else (i.e., pancreas, lungs)**.
- Failure to secrete Cl^- from the pancreas and lungs leads to a buildup of Cl^- inside the pancreatic acinar cells and alveolar cells, respectively.
- Buildup of intracellular chloride means increased negative charge inside the cell.
- In order to balance charge, extracellular sodium within the pancreatic ducts and alveoli moves into the cell **via ENaC** to balance intracellular charge.
- Since H_2O follows Na^+ , ↑ H_2O reabsorption leads to viscous luminal secretions.
- This desiccation (drying up) is called **inspissation**.
- This is why there are thickened secretions in CF.

Your next question might be, “Well that’s great, but how the fuck does the USMLE actually test that?”

Great, I’ll tell you:

You’ll literally get a question that sounds like CF (discussed below), then they’ll simply ask you for which mechanism regarding ion shift occurs in CF, and **the answer is ↑ activation of ENaC**.

You need to know where the misfolded channel ends up

One of the highest yield points regarding cystic fibrosis is that mutated *CFTR* leads to the production of CFTR channel that is **retained as a misfolded protein in the rough endoplasmic reticulum (RER)**.

The USMLE is obsessed with asking about this. “Defective chloride channel found in cell membrane” is **100% the WRONG answer**.

Now clearly the RER is in the cytosol, so occasionally the answer might also be “misfolded protein sequestered in cytosol.” You get the point.

There is one special case that is an exception that I discuss in treatments below.

Things move the opposite direction in the sweat glands

- Whereas Cl^- is secreted in the pancreas and alveoli, it’s reabsorbed in the sweat glands.
- Normal sweat losses are hypotonic. In CF, they’re **isotonic**.
- This leads to ECF (extracellular fluid) contraction because failure of ↑ in ECF tonicity fails to draw out ICF (intracellular fluid) to compensate.
- The contraction stimulates RAAS (renin-angiotensin-aldosterone system).
- ↑ aldosterone-mediated distal renal K^+ & H^+ wasting can lead to **contraction alkalosis**.

If they ask about which diuretics can cause effects similar to CF, **the answer is loop diuretics**.

An extremely HY factoid regarding diagnosis

- Diagnosis is made via **sweat chloride testing** indicating $> 60 \text{ mEq/L}$ of chloride in the sweat.
- **The sweat Cl^- test is more diagnostic of CF than genotyping**.

You might say, “Well how the fuck is that possible? How could anything be more accurate than having evidence of the mutation in the gene itself?”

This is because the *CFTR* gene can incur a myriad of mutations that lead to disease (**allelic heterogeneity**; different disease alleles can cause same disease), thereby ↓ sensitivity (↑ false-negatives) of genotyping.

In other words, there are so many possible mutations that can cause CF that genetic laboratories often run “common panels,” which will screen for the most frequent mutations spanning, e.g., 90-96% of known CF mutations. In contrast, sweat chloride is 100% accurate. If a patient has CF, he or she will almost certainly have a positive sweat chloride test.

- Neonates can be screened for a positive blood **immunoreactive trypsinogen**.
- If positive, the neonate requires a confirmatory sweat chloride test, where topical pilocarpine (muscarinic agonist) stimulates the sweat secretion.
- Rarely in patients who have a non-diagnostic sweat chloride test and negative genotyping, a **nasal transepithelial potential difference (TEPD) test** can be performed.

In CF, there is a more negative transepithelial potential difference

- TEPD merely refers to the charge gradient between the external and internal cell surfaces of respiratory epithelium.
- Since Na^+ is reabsorbed, less positive charge remains on the external **cell surface**, thereby causing the transepithelial potential difference to be more negative.
- A nasal TEPD $< 40 \text{ mV}$ is considered positive.

Pulmonary manifestations

- Cystic fibrosis is associated with **increased frequency of pulmonary infections**. Although various organisms can cause infection, *Pseudomonas* and *Staph* infections are notably more common.

How to break 260 on Step 1:

Pseudomonas is the answer as the most likely organism **if over age 10**.

Under age 10, *S. aureus* exceeds *Pseudomonas*.

The frequencies cross at age 10.

In other words: 8-year-old with CF has pneumonia. Most likely organism? **Answer = *S. aureus*, not *Pseudomonas***. Woah, craziness.

- Cystic fibrosis is the most common cause of **bronchiectasis** in the USA. Bronchiectasis can cause clubbing. So CF is often associated with clubbing.
- **Nasal polyps** are often seen in patients with CF. (Seemingly weird detail that is exceedingly HY)

Exocrine pancreas insufficiency causes fat-soluble vitamin malabsorption

- Since the pancreatic secretions are inspissated, pancreatic enzyme secretion is less efficient and signs of **malabsorption** are common.
- Fat-soluble vitamin (**A, D, E, K**) and **B12** deficiencies are common. (All of those blue vitamins link to unique posts btw)
- So be on the lookout for any symptoms of those nutrient deficiencies, e.g., nyctalopia (A), rickets (D), hemolysis (E), ↑ PT/aPTT (K), megaloblastic anemia (B12), and neurological findings (E and B12).

Endocrine pancreas insufficiency can cause diabetes mellitus

- Diabetes mellitus is one of the most common morbidities of CF, occurring in ~20% by adolescence and ~40-50% by adulthood.
- (Obtained those %s from this highly cited American Diabetes Association article [here](#))

Failure to pass meconium in the first 24 hours of life is super HY

- **Failure to pass meconium in the first 24 hours of life** is most commonly due to cystic fibrosis (and less commonly Hirschsprung disease).
- In CF, this failure to pass meconium is given a special name called **meconium ileus**, where inspissated meconium plugs the ileum.

Some notable treatments for CF

- **N-acetylcysteine** softens mucous (N-acetylcysteine has an -SH that reacts with -S-S- bonds in mucous).
- **Guaifenesin** ↑ expectoration / clearance of mucous.
- **Dornase-α** is a recombinant deoxyribonuclease that breaks down DNA left over from leukocytic debris within mucous. It's important to associate CF with **lots of nucleic acid plugging the airways**.

Ivacaftor is a special drug you must know

- One type of mutation leading to CF, the G551D missense mutation, leads to a glycine that is replaced by an aspartic acid at position 551.
- **This enables the CFTR channel to make it to the cell surface, in contrast to sequestration in the RER/cytosol.**
- The CFTR channel is still defective; it's just merely at the correct location on the cell surface.
- **Ivacaftor** is a CFTR modulator that binds to this misfolded channel and increases the probability it will open.

USMLE likes to ask a couple weird genetics questions about CF

- We already talked about how CF is AR and the *CFTR* gene is on chromosome 7.
- However the USMLE wants you to know that if a phenotypically normal patient has a sibling with an AR condition (e.g., CF) when both parents are carriers, **his or her chance of being a carrier is TWO-THIRDS**. And further, two people in this category mating would have a **one-ninth** chance of having a child with an AR condition.

2/3 chance of being carrier

AA	Aa
Aa	aa

2x Aa / 3 remaining possibilities

If someone who is **phenotypically normal** (i.e., does not have the disease) has a sibling with an AR disorder (e.g., CF), there is a 2/3 chance he or she is a carrier because it's impossible he or she is "aa" if phenotypically normal.
Got it?

Guy has a sibling with CF. His wife does not have a family history. The carrier rate in the general population is 1/50. What is the chance they have a child with CF?

- His chance of being a carrier is 2/3
- Her chance is 1/50
- $(2/3)(1/50)$ chance they both are carriers $\times 1/4$ chance their kid would be "aa" = $(2/3)(1/50)(1/4) = 1/300$ chance.

Not bad right? But if you didn't know about this 2/3 "factoid" beforehand, you'd be sitting there on the real exam like, "Wait, wtf, why is this weird. Let me think about this shit."

- If you get a question where they tell you someone with CF has **two copies of an "exceedingly rare" mutation no one's ever heard of**, and they want to know the mechanism for disease, **the answer = uniparental isodisomy**.
- This means the individual somehow got two copies of the same allele from the same parent.
- They will also list uniparental heterodisomy as an answer (receiving two different alleles from the same parent), but this can't be correct because if this were the case, the parent would also have the disease.
- If you have two copies of an allele that is "one in ten-million," it's absurdly unlikely each parent carried that allele and passed it.

CBAVD and CF

- Another really important point is cystic fibrosis in relation to **infertility**.
- Cystic fibrosis is known to cause **congenital bilateral absence of the vas deferens (CBAVD)** in men.
- Even asymptomatic carriers have an increased likelihood of CBAVD and infertility.
- Because the vas deferens is absent bilaterally, **there are NO sperm** seen in a sample of ejaculate.

Kartagener syndrome (primary ciliary dyskinesia)

The USMLE is obsessed with the contrast between Kartagener syndrome and cystic fibrosis in regard to infertility

- A disorder characterized by **immotile, dysfunctional cilia**, resulting in sperm immotility and defective fallopian tube-mediated ovum transport.
- This leads to male and female infertility, as well as increased risk of ectopic pregnancy.

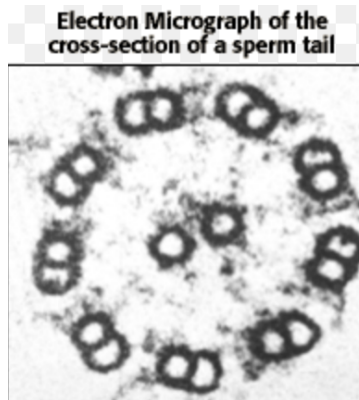
A couple has been unsuccessful achieving pregnancy after 12 months of regular intercourse. The male has a heavy history of respiratory tract infections. His semen sample is analyzed. Are there sperm seen in the sample?

Yes, there are sperm, but they are immotile → **Kartagener syndrome**

No, there are no sperm seen in the sample. → **Cystic fibrosis (CBAVD)**

USMLE gets pedantic about the ciliary defect

- The cilia are immotile because of a **dynein arm defect**.
- Dynein is a protein that enables proper ciliary motility.
- **A cilium is composed of a 9+2 arrangement of microtubules.**
- In other words, a cilium is larger than a microtubule.



Electron micrograph of a cross-section of a cilium. You can see the 9 + 2 arrangement of microtubules. The USMLE has been known to show EMs like this.

Kartagener is associated with situs inversus

- You need to know that Kartagener syndrome is associated with situs inversus, where the internal organs are on the opposite side of the body.
- They might tell you the apex beat is palpated in the 5th intercostal space, just medial to the right midclavicular line.

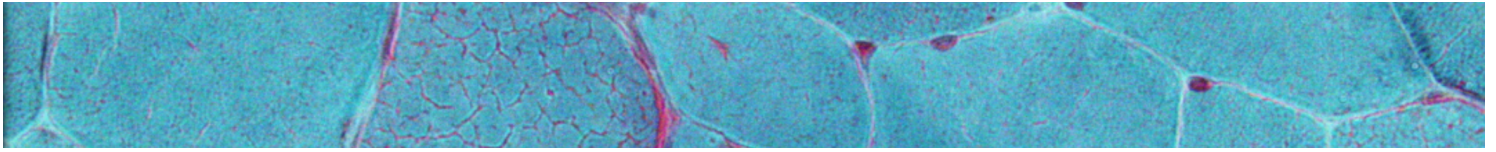
If they don't overtly tell you there is dextrocardia (or full-blown situs inversus), they might show you a CXR with the cardiac shadow on the left side of the image (right side of the body).

Pulmonary infections are characteristic

- As mentioned under infertility above, another common finding is **chronic respiratory tract infections** or bronchiectasis, due to impairment of mucociliary clearance.

1. What is the inheritance pattern of cystic fibrosis and what is the chromosome number?

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BIOCHEMISTRY

Down, Edward, & Patau syndromes

by MEHLMANMEDICAL

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Down syndrome (trisomy 21)

Mechanisms are HY

- The vast majority of the time (>95%), the syndrome is caused by meiotic nondisjunction of the **maternal** chromosome 21, leading to an ovum with two copies of chromosome 21 (the male sperm adds the third upon fertilization).
- Roughly <5% of the time, Down syndrome is due to **Robertsonian translocation**.
- Finally, about <1% of the time, Down syndrome is due to **post-fertilization mitotic error, leading to mosaicism**.

Meiotic nondisjunction

- It is known that **advanced maternal age** is associated with increased risk of meiotic nondisjunction, but the USMLE wants you to know that it is age thirty-five, **NOT forty**, that is the threshold age for significance.
- At age 35, risk is 1/350.
- At age 40, risk is 1/100.
- At age 49, risk is 1/10.
- Most common cause of mental retardation across the entire population is fetal alcohol syndrome (FAS), however over age 40 it is Down syndrome.

Robertsonian translocation

- Firstly, an **acrocentric chromosome** is when the centromere that joins the short (p) and long (q) arms is located near one end, rather than close to the middle.
- A Robertsonian translocation is when two chromosomes' q-arms join together at a centromere, and the two p-arms are lost.
- In Down syndrome, this occurs between **chromosomes 14 and 21**. This is written as **t(14q;21q)**.
- If a child has Down syndrome, **one of the parents**, instead of having two separate copies of chromosome 21, has one of his or her chromosome 21s attached to one of his or her chromosome 14s.
- The total amount of genetic material in the parent is normal (balanced), so he or she doesn't have any pathology, but if the abnormal chromosome 14 is passed to the offspring, a trisomy can occur.

Mosaicism

- When only a fraction of the individual's cells contain the trisomy, and the other fraction is normal.
- The mechanism for this cannot possibly happen during meiosis, because if it did, all of the child's cells would contain the trisomy.
- So if they ever mention a case of a mosaic Down syndrome patient, **the answer is always post-fertilization mitotic error**.

- The above underlined point is exceedingly HY!

Outward features

- **Epicanthal folds** (down-turning of medial canthus of eyes)
- **Slanted palpebral fissures** (refers to the elliptical space between the eye's lateral and medial canthi)
- **Flat facies** (lack of anterior projection of profile, often with a very flat nose).

Flat facies are a major distinguishing feature in Down syndrome. Patau and Edward syndrome will not present with flat facies.

- **Brushfield spots** (small white spots found in the periphery of the iris)
- The hands often show a **single palmar crease**, also known as a **Simian crease**.
- However it should be noted that the single palmar crease, whilst seen in ↑ frequency in Down syndrome, is **NOT** pathognomonic and **can also be seen in the general population**. For instance, if they mention a single palmar crease + **elongated philtrum**, the answer is FAS, not Down.

Multi-system defects

- There are classic **endocardial cushion defects** in the heart (often resulting in **atrioventricular septal defect (AVSD)**, or **ostium primum-type atrial septal defect**).
- Down patients also tend to have a cleft on the mitral valve (and sometimes the tricuspid valve), which **increases the risk of mitral and tricuspid regurgitation**.
- Increased risk of **pulmonary hypertension** and pulmonary artery malformations.

If they ask you blindly what kind of cardiac defect is most likely in Down syndrome (i.e., VSD, ASD, AVSD), **choose AVSD**.

If they ever ask you about the mechanism of cardiac defects in Down syndrome, **the answer is failure of neural crest cell migration**, since the heart's endocardial cushions develop from neural crest.

- Gastrointestinally, there is increased risk of **tracheoesophageal fistula**, **duodenal atresia**, and **Hirschsprung disease**.
- Hematologically, there is increased risk of **ALL and AML**.
- Hypothyroidism (↑ TSH)
- Recurrent otitis media + hearing impairment due to **eustachian tube dysfunction**

One of the most heavily tested clinical features of Down syndrome is that it leads to **early Alzheimer disease** (i.e., 30s-40s). This is because one of the genes for β-amyloid production is on chromosome 21.

Down syndrome and laboratory findings in pregnancy

- **First trimester triple screen** (11-13 weeks) shows ↑ **nuchal translucency**, ↓ **PAPP-A**, and ↑ **beta-hCG**
- ↓ **PAPP-A** in particular is exceedingly HY.
- Nuchal translucency refers to the amniotic fluid accumulation behind the fetal neck; it should normally be a thin slit, but in Down syndrome it is almost always widened.

There is also a **hypoplastic or absent nasal bone** seen on first trimester screen.

This makes sense because of the flat facies seen clinically.

This detail is very HY.

- **Second trimester quad screen** (16-18 weeks) shows ↓ **AFP**, ↓ **estriol**, ↑ **β-hCG** and ↑ **inhibin A**.
- One way to remember this combination is by first recalling that in neural tube defects, AFP is elevated. In contrast, it's Down in Down syndrome.
- Estriol is a reflection of **fetal well-being**. Then you can say, "A child with Down syndrome is not well so estriol must be down."
- So if you remember those two are down, then you'll be able to recall that β-hCG and inhibin A must be the ones that are up.

First trimester triple screen (11-13 weeks):

- ↑ nuchal translucency | ↓ PAPP-A | ↑ beta-hCG
- Nasal bone hypoplastic or absent on ultrasound

Second trimester quad screen (16-18 weeks):

- ↓ AFP | ↓ estriol | ↑ β-hCG | ↑ inhibin A

Prenatal testing

- **Chorionic villus sampling (CVS)**
 - Can be performed at ~10-12 weeks.
 - A sample of placental tissue is retrieved via an ultrasound-guided needle, either transcervically or -abdominally.
 - If adequate sample is obtained, there is a near 100% diagnostic accuracy for Down syndrome (and many other disorders).
 - Risk of iatrogenic abortion (fetal demise) has been ubiquitously reported in the literature as on the magnitude of ~1%.
- **Amniocentesis**
 - Generally performed ~14-16 weeks.
 - Ultrasound-guided needle is inserted transabdominally into the amniotic sac to retrieve free-floating fetal DNA.
 - Adequate sample yields near 100% diagnostic accuracy.
 - Iatrogenic abortion (fetal demise) can occur ~0.5% of the time, but the literature varies as far as the range. It is definitive, however, that amniocentesis carries lower risk than CVS.
- **Cell-free DNA**
 - Can be performed ~10 weeks gestation.
 - Also referred to as **NIPD** (non-invasive prenatal diagnosis)
 - Test involves nothing more than merely drawing maternal venous blood and analyzing free-floating fetal DNA that normally crosses the placenta in trace amounts.
 - Newest test (as compared to CVS and amniocentesis), but also most expensive, and many clinics and regions don't offer it.
 - Accuracy is near 100%, and risk of iatrogenic abortion is near zero.

Edward syndrome (trisomy 18)

Edward syndrome is not tested nearly as frequently as Down's, but there are a few key points that show up from time to time that you need to know.

- Classic characteristics are **low-set ears, micrognathia, prominent occiput, clenched hands, and rocker bottom feet**.
- Other typical features (although not pathognomonic) are **omphalocele**, Meckel diverticulum, and gut malrotation.

Whereas most Down syndrome patients survive into adulthood, those with Edward (trisomy 18) or Patau syndrome (trisomy 13) tend to die within the first twelve months of life.

- In contrast to Down syndrome, AFP, estriol, β-hCG and inhibin A are all down.

Although low-set ears are almost always mentioned for Edward syndrome, trisomy 18 is NOT associated with flattened facies.

Down syndrome is once again associated with flattened facies.

If you get a question mentioning low-set ears, flattened facies and clubbed feet, this is a classic external presentation for **Potter sequence** (renal agenesis + pulmonary hypoplasia) secondary to oligohydramnios, NOT Edward syndrome.

In other words:

Prenatal ultrasound shows:

Flattened facies + hypoplastic nasal bone + ↑ nuchal translucency = **Down syndrome**

Low-set ears + rocker bottom feet + prominent occiput +/- omphalocele = **Edward syndrome**

Low-set ears + clubbed feet + flattened facies = **Potter sequence**

Edward doesn't have flattened facies, so if they tell you there's low-set ears and abnormal feet, don't automatically jump on Edward. Be mindful for Potter sequence.

Patau syndrome (trisomy 13)

- Presents classically with **holoprosencephaly**, **cleft lip/palate**, **polydactyly**, and omphalocele.
- AFP, estriol, β -hCG and inhibin A are often all normal, however these values are practically never addressed in USMLE questions because they vary.
- USMLE questions on Patau syndrome tend to focus on the above bold findings (**notably holoprosencephaly**).

To that effect, if you get a question on holoprosencephaly, the top three DDX tested on Step1 are **severe fetal alcohol syndrome** (most common cause), **Patau syndrome**, and **homeobox gene mutation**.

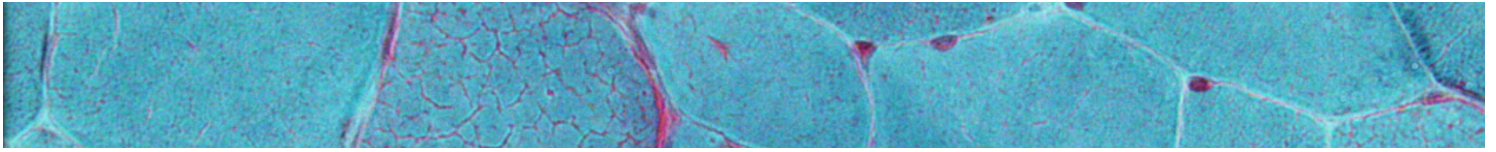
Similarly, if you get a question mentioning cleft lip/palate, the top three USMLE Step1-tested associations are **DiGeorge syndrome**, **Patau syndrome**, and **vitamin A teratogenicity** (i.e., maternal use of isotretinoin).

—

1. What are the three mechanisms via which someone can be born with Down syndrome?

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Duchenne vs Becker muscular dystrophy

by MEHLMANMEDICAL

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Inheritance pattern and molecular understanding are really HY for USMLE

- Both Duchenne and Becker are **X-linked recessive**.
- Caused by mutations in the **dystrophin** gene (*DMD*).
- Dystrophin is a large **cytoskeletal protein** inside skeletal muscle that stabilizes the cytoskeleton with the extracellular matrix.
- Dystrophin binds to a transmembrane protein called **beta-dystroglycan**.
- The dystroglycan-dystrophin complex is necessary for normal skeletal muscle cell integrity.

USMLE wants you to know that Duchenne is usually caused by a **frameshift mutation** (i.e., 1 or 2 bp deleted or inserted).

In contrast, Becker is usually **not** caused by a frameshift (i.e., a missense mutation, or deletion/insertion in repeats of 3 bp, etc.).

Age of onset and the Gower maneuver

- You need to know that **Duchenne is worse than Becker**.
- Questions on Duchenne will almost always mention a **young boy**, whereas for Becker they'll almost always mention a **teenager or adult**.
- Boys who have **Duchenne** classically exhibit the **Gower maneuver**. This is described as **walking backwards with the arms in order to stand up**. You will not see the Gower maneuver being described in a patient with Becker; on the Step1, this is Duchenne only.

Pseudohypertrophy and affected muscles

- All hypertrophy that occurs is followed by **pseudohypertrophy**, which is **fibroadipose deposition** in the muscle.



Source: Richard P. Usatine, Mindy Ann Smith, Heidi S. Chumley, Camille Sabella, E.J. Mayeaux, Jr., Elumalai Appachi: *The Color Atlas of Pediatrics*: www.accesspediatrics.com Copyright © McGraw-Hill Education. All rights reserved.

- Despite the seemingly enlarged muscle size, patients progress to profound weakness.
- Asymmetrical weakening of paraspinal muscles leads to kyphoscoliosis.
- The USMLE-tested cause of death from both diseases is **cardiomyopathy/heart failure**.

Pseudohypertrophy = **fibroadipose replacement of the muscle**.

Biopsy shows fibrous and fatty tissue; it also shows **variation in fiber diameter** and ↑ # of internalized nuclei + fiber regeneration / degeneration.

- The muscular dystrophies tend to affect pelvic girdle muscles and calves first.
- If they ever ask you which location the weakness starts first, and calves and hips are both answers, hips are correct over calves.
- Most students get this wrong because these patients are classically photographed for having massively hypertrophied calves, but the calves are typically not the first place affected.

Miscellaneous

- One last point about the *DMD* gene is that it is the **longest human gene**. This means if they ever ask you which gene would be most likely to undergo a **spontaneous mutation**, the answer is *DMD*.

—

1. What is the inheritance pattern of Duchenne and Becker muscular dystrophies?

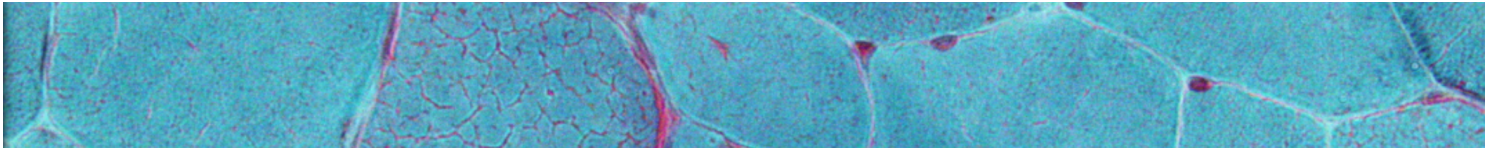
- ☐ XD
- ☐ XR
- ☐ AR
- ☐ AD

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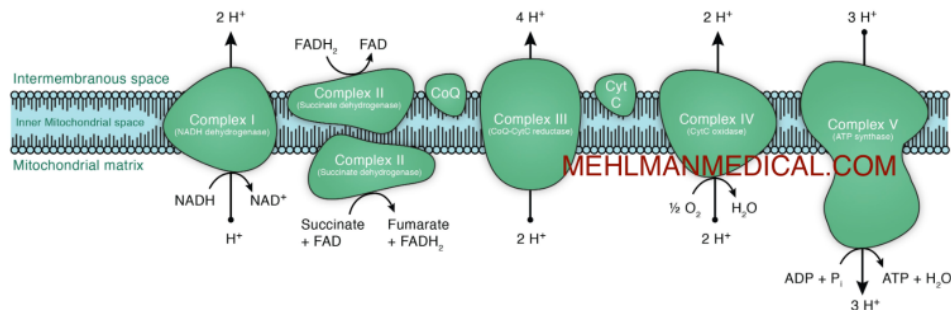
Electron transport chain

by MEHLMANMEDICAL

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The electron transport chain (ETC) functions to generate ATP from a high-proton gradient established in the intermembrane space in the mitochondria.

ETC → lots of protons in mitochondrial intermembrane space → increased ATP-producing turbine activity (Complex V; ATP synthase).

Here are some facts the USMLE is known to test about the ETC:

2,4-dinitrophenol, ethanol, aspirin, and thermogenin are uncoupling agents. (DEATH)

An uncoupling agent destroys the H^+ gradient within the inner mitochondrial membrane necessary for ATP synthesis, so compensatory over-activation measures to restore the H^+ gradient yield heat.

Uncoupling agent → protons leak back into inner mitochondrial space (i.e., do not go through Complex V) → more protons need to be pumped into intermembrane space to achieve same ATP production → more O_2 required to generate same # of ATP →

Uncoupling agents ↑ O_2 consumption / ATP production ratio

Uncoupling agents ↑ CO_2 production / ATP production ratio

Cyanide (CN^-) causes inhibition of electron transfer to molecular oxygen.

Treatment = amyl nitrite + sodium thiosulfate

—

Methemoglobinemia = “chocolate brown” blood

Fe³⁺ hemoglobin cannot bind oxygen, so saturation is decreased.

—

In contrast to chocolate brown blood of methemoglobinemia,

Cherry red blood = bright red lips/face/nail beds = CO poisoning.

CO poisoning causes **metabolic acidosis** (↓ bicarb) because ↓ O₂ delivery to tissues results in lactic acidosis.

You also need to know (random as fuck):

Thermogenin is a protein found in the mitochondria of **brown fat (brown adipose tissue)** and serves to keep neonates (and hibernating animals) warm. **It is also an uncoupling agent.**

The USMLE might tell you that a neonate needed surgery for removal of a mass and that the physician needed to remove some of the surrounding fat in the process. **If they ask you about a potential post-surgery complication, the answer is hypothermia** because of removal of brown fat. Clinically, the scenario is unlikely and completely outrageous and ridiculous, but this is how the USMLE tests thermogenin.

Finally (low-yield, but have been known to show up once in a blue moon):

Rotenone inhibits **Complex I** (NADH dehydrogenase)

Antimycin A inhibits **Complex III**

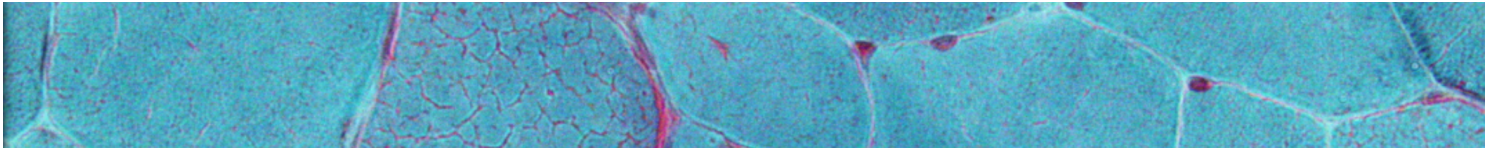
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1. If you consume alcohol, which of the following is true? (Select all that apply)

- ☐ Increases CO₂ production / ATP synthesis ratio
- ☐ Decreases CO₂ production / ATP synthesis ratio
- ☐ Increases O₂ consumption / ATP synthesis ratio
- ☐ Decreases O₂ consumption / ATP synthesis ratio
- ☐ Increases proton flow through ATP synthase (complex V)

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Familial dyslipidemias

by MEHLMANMEDICAL

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Familial dyslipidemias

There are three that you need to know for the USMLE: **type I (hyperchylomicronemia)**, **type II (hypercholesterolemia)** and **type IV (hypertriglyceridemia)**. There are plenty of other types but the USMLE won't assess them. But hey, who's to say you couldn't score a 290.

So for the sake of the USMLE, know this concise chart:

Disorder	Hyperchylomicronemia	Hypercholesterolemia	Hypertriglyceridemia
Lab report	↑ Chylomicrons + TGAs	↑ LDL	↑ TGAs
Mechanism	Deficiency of Apo-CII or LPL	Deficiency of LDL receptor	↑ hepatic production of VLDL

You can remember hyperchylomicronemia is type I because chylomicrons are the 1st out of the intestines. This disorder is due to deficiency of either Apo-CII or LPL (lipoprotein lipase). Apo-CII and LPL are your USMLE buzzwords for type-I familial dyslipidemia.

If you are ever asked about which apolipoprotein allows for delivery of TGAs to tissues, the answer is CII.

Apo-CII is a cofactor for LPL. So **both** are required for chylomicron release of TGAs into tissues.

The important point about hyperchylomicronemia is that **cholesterol and triglycerides** (TGAs) are increased. Chylomicrons contain large amounts of cholesterol and TGAs.

When they are absorbed by the gut, they travel to peripheral tissues, where they release TGAs. The release of TGAs into the tissues requires apolipoprotein (Apo) CII and lipoprotein lipase (LPL).

USMLE lab report shows high TGAs **and** LDL → answer = Deficiency of Apo-CII or LPL

If you ever see a question that asks about the location of LPL, and both adipocytes and endothelial surface are answers, **endothelial cell surface** is correct.

It is at the endothelial surface that LPL converts TGAs into three phospholipids and monoacylglycerol; only these individual components can be absorbed, not the fully assembled TGA itself, so LPL must act at the vascular endothelium before the TGA can enter the adipocyte.

For familial hypercholesterolemia, one of the highest yield points is that it is **autosomal dominant**.

The other really high-yield point is that if they give you an LDL level of ~300s mg/dL, the patient is **heterozygous**, i.e., he or she has a deficiency, rather than absence, of LDL receptors, and generally presents in adulthood; if they give you an LDL level of ~700s mg/dL, the patient is **homozygous** and has near absence of LDL receptors. The latter will present as a child or adolescent with an MI.

Xanthomas of the Achilles tendon or eyelid are a fairly standard presenting feature of this disorder.

300s mg/dL = heterozygous; 700s mg/dL = homozygous

Treatment is **statins** (e.g., atorvastatin), which **competitively and reversibly inhibit HMG-CoA reductase** (the rate-limiting step in cholesterol synthesis).

This leads to **increased HMG-CoA reductase mRNA expression** (liver increases gene transcription to compensate for inhibited enzyme function). This is an answer on one of the NBME exams.

Statins also indirectly lead to increased synthesis of LDL receptor expression on vascular endothelium. This is because decreased synthesis of cholesterol by the liver leads to more being pulled out of the blood to compensate.

Statins are **competitive and reversible**, meaning they **increase Km but do not change Vmax**. The dose-response curve is **shifted to the right, not down**. Sounds pedantic, but it's shown up in a question.

A side note about statins is that they are the best at reducing morbidity/mortality because **they have an antioxidant effect on endothelial cells that transcends the mere LDL-lowering effects**.

Ezetimibe, for instance, which directly blocks cholesterol absorption in the small bowel, doesn't decrease mortality, despite lowering LDL. By all means there are many lipid-lowering agents that could be mentioned, but the USMLE likes you to know the MOA of ezetimibe for whatever reason.

Familial hypertriglyceridemia presents with an isolated increase in TGAs. They might mention pancreatitis in the vignette, but in general, they'll drive the fact that only TGAs are up, not cholesterol, and then they'll ask about the mechanism. LPL or Apo-CII deficiency might be listed, but they're wrong because deficiency of either would result in elevated cholesterol as well (as we discussed with hyperchylomicronemia). **The mechanism of type IV is a simple hepatic overproduction of VLDL**, which is composed predominantly of TGAs.

Fibrates (e.g. fenofibrate, gemfibrozil) are the answer for the best drugs for lowering TGAs. However they can cause **myopathy** and **hepatotoxicity**. **The risk of myopathy is augmented when combined with statins because of cytochrome (CYP) inhibition**. This latter point is an answer on one of the NBMEs.

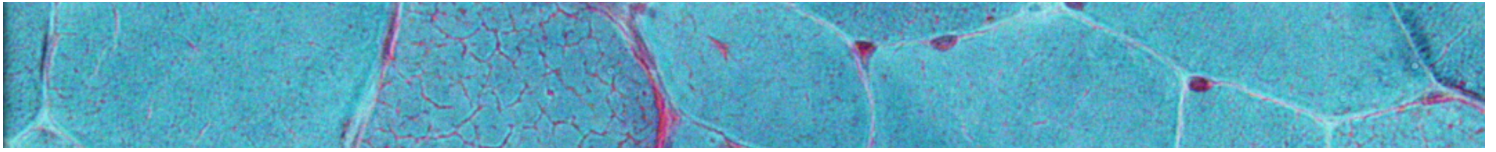
Ezetimibe directly inhibits cholesterol absorption in the gut.

↑ LDL cholesterol = MI ↑ TGAs = pancreatitis

Another important point is that **hypertriglyceridemia is strongly linked to pancreatitis**. This means if you get a question that mentions ↑ TGAs but normal cholesterol, and then they ask you what is the most likely symptom, and both chest pain and abdominal pain are answers, **abdominal pain is correct over chest pain**. **Chest pain is the WRONG answer in this scenario**. This isn't to say that clinically a patient couldn't get chest pain, but **PANCREATITIS** resulting in abdominal pain is what the USMLE wants you to assume is more likely in isolated triglyceridemia.

1. 22 year-old has lab report with increased TGAs; LDL is normal. What's the mechanism for this patient's condition?

- ☐ Deficiency of apolipoprotein CII or LPL
- ☐ Increased hepatic production of VLDL
- ☐ Deficiency of LDL receptor



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Fatty acid metabolism

by MEHLMANMEDICAL

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You need to know fatty acids are broken down into two-carbon units called acetyl-CoA.

If you have a six-carbon fatty acid, that will be broken down into three acetyl-CoAs. (Rocket science)

However what if the fatty acid is odd-chain?

We will never get one-carbon units. But we will get three-carbon units, called propionyl-CoA.

If our fatty acid is, e.g., seven carbons, we'll therefore get two acetyl-CoA + one propionyl-CoA.

Fatty acid is 6 carbons → becomes 3 acetyl-CoA

Fatty acid is 7 carbons → becomes 2 acetyl-CoA + 1 propionyl-CoA.

Then, Propionyl-CoA → methylmalonyl-CoA → succinyl-CoA in the TCA cycle.

You also need to know that **carnitine** is necessary for **degradation** of fatty acids into acetyl-CoA. Just memorize it.

Carnitine sits in the inner mitochondrial membrane and is inhibited by malonyl-CoA.

Malonyl-CoA is normally a molecule that is produced when fatty acids are synthesized. So if the goal is to make more fatty acids and malonyl-CoA levels subsequently go up, then carnitine will naturally be inhibited.

The USMLE will literally ask you which molecule is responsible for negatively regulating the breakdown of fatty acids, and the answer is malonyl-CoA.

What inhibits fatty acid breakdown? **Malonyl-CoA**

This is important because the USMLE assesses **carnitine deficiency**.

If carnitine is deficient, then the patient will have **hypoketotic hypoglycemia**, but no acyl-CoA (not the same as acetyl-CoA) buildup in the mitochondria.

Hypoketotic hypoglycemia. Acyl-CoAs present in mitochondria? **No.** → **carnitine deficiency**

Hypoketotic hypoglycemia. Acyl-CoAs present in mitochondria? **Yes**. → **acyl-CoA dehydrogenase deficiency**

The above lines are what you need to memorize, but if you want more explanation:

Fatty acids are first converted to acyl-CoAs in the cytosol before being shuttled into the mitochondria via carnitine. The acyl-CoAs then disassemble in the mitochondria and are converted to acetyl-CoAs.

If **acyl-CoAs are found in the mitochondria**, then it's **not possible that carnitine is deficient** because the acyl-CoAs wouldn't have been able to enter.

So if you have **hypoketotic hypoglycemia with acyl-CoA** buildup in the mitochondria, you instead of **acyl-CoA dehydrogenase deficiency**, since this enzyme enables the breakdown of acyl-CoAs in the mitochondria.

One of the highest yield, but seemingly weird, biochemistry points on USMLE Step1:

Acetyl-CoA is a (+) regulator of pyruvate carboxylase, an enzyme necessary for $\text{PEP} \rightarrow \text{OAA}$ in gluconeogenesis. Therefore $\downarrow$ production of acetyl-CoA = $\downarrow$ gluconeogenesis = $\downarrow$ glucose production

$\downarrow$ acetyl-CoA $\rightarrow$ $\downarrow$ OAA production $\rightarrow$ $\downarrow$ PEP production $\rightarrow$ $\downarrow$ glucose production $\rightarrow$ forces available/limited acetyl-CoA to be used for ketogenesis

—

Reye syndrome (never give aspirin to children with fever, especially if suspected viral etiology) is caused by disrupted fatty acid beta-oxidation in the mitochondria of virus-infected cells.

—

1. A 9-carbon fatty acid will be metabolized into how many acetyl-CoA and propionyl-CoA?

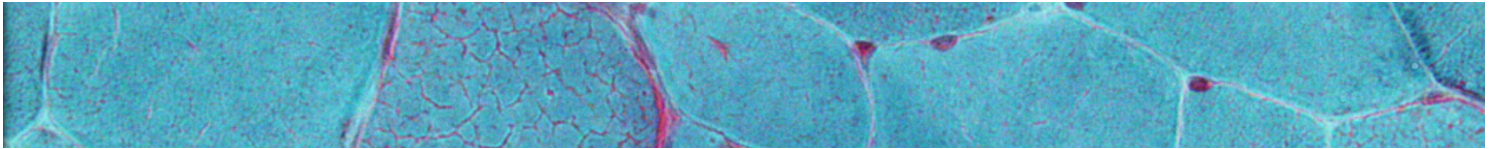
- ☐ 4 acetyl-CoA; 1 propionyl-CoA
- ☐ 3 acetyl-CoA; 1 propionyl-CoA
- ☐ 1 acetyl-CoA; 4 propionyl-CoA
- ☐ 1 acetyl-CoA; 3 propionyl-CoA

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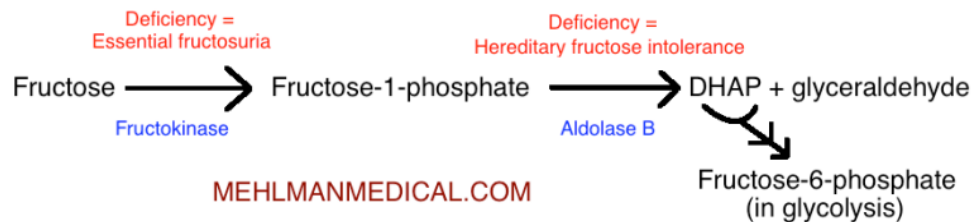
Fructose disorders

by MEHLMANMEDICAL

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The fructose disorders on the USMLE are presented in vignettes as an infant who has just been introduced to **fruit, honey, or juice**.

Essential fructosuria = deficiency of **fructokinase** = asymptomatic presentation

Hereditary fructose intolerance = deficiency of **aldolase B** = severe presentation

A USMLE question assessing you on essential fructosuria will give you a completely normal/asymptomatic infant who has **reducing sugar in the urine**. This is due to fructokinase deficiency.

When aldolase B is deficient, there is a buildup of fructose-1-phosphate, which leads to **jaundice, cirrhosis, and hypoglycemia**.

Questions also like you to know that the *reason* the Sx are so severe with hereditary fructose intolerance is because of trapping of hepatic phosphate as fructose-1-phosphate.

For the fructose (and **galactose**) disorders, deficiency of the more downstream (second) enzyme causes the severe presentation. **This is because of phosphate trapping in the liver**. Buildup of fructose-1-phosphate means more phosphate is tied up in the form of that intermediate.

A patient with a fructose disorder needs to **avoid table sugar**, since this is sucrose, which is catabolized to glucose + fructose.

—

1.

a) What are the two fructose disorder enzymes? (2 points)

b) What are the names of the two respective conditions caused by these enzyme deficiencies? (2 points)

c) Deficiency of which is worse? (1 point)

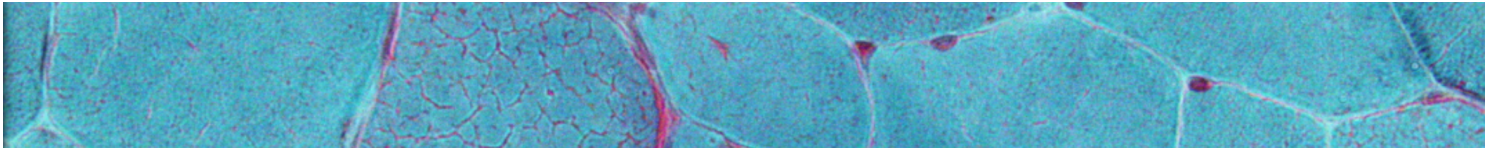
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HY USMLE Q #940 – Biochemistry

January 1, 2024



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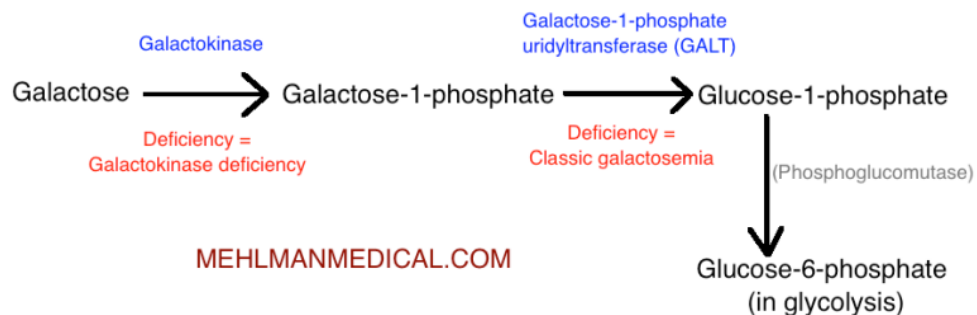
Galactose disorders

by MEHLMANMEDICAL

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Galactokinase deficiency = mere deficiency of **galactokinase** = milder presentation

Classic galactosemia = deficiency of **galactose-1-phosphate uridylyltransferase (GALT)** = severe presentation

Galactokinase deficiency will show up in questions as infantile cataracts and galactose in the urine. That's it. They'll give you **an infant who recently started breastfeeding** who now has problems seeing or who has leukocoria.

The USMLE likes to say that **"a reducing sugar" was detected in the urine.**

To that effect, in fructose disorders, they'll say the same thing. Galactose and fructose are not detected on urine dipstick because that test is specific for glucose, but they are still detected as reducing sugar in the urine.

Urine dipstick is specific for glucose and won't detect galactose or fructose. But the USMLE will say "reducing sugars in the urine" for galactose (and fructose) disorders.

Rarely the question might mention that the infant doesn't develop social smile or track objects, so be aware that mild cognitive delay *can* be seen, but in general, visual problems + reducing sugar in the urine in an otherwise benign presentation = galactokinase deficiency.

In contrast, classic galactosemia will present severely.

Look for **hepatosplenomegaly, jaundice, and mental impairment.**

↓ vision + reducing sugar in urine. Does the child have jaundice + HSM + severe mental impairment?

No, there's no jaundice or HSM. There's no (or mild) mental impairment. → Galactokinase deficiency

Yes, there's jaundice, HSM, and severe mental impairment. → Classic galactosemia

USMLE questions wanting you to distinguish between galactokinase deficiency and classic galactosemia will always give you hepatosplenomegaly and jaundice if the answer is classic galactosemia. Mental impairment *can* be seen in galactokinase deficiency, but if the question does illustrate developmental delay, it will always be severe in classic galactosemia, whereas it will only be mild in galactokinase deficiency.

For the galactose (and [fructose](#)) disorders, deficiency of the more downstream (second) enzyme causes the severe presentation. **This is because of phosphate trapping in the liver.** Buildup of galactose-1-phosphate means more phosphate is tied up in the form of that intermediate.

The child must stop breastfeeding if a galactose disorder is diagnosed because lactose in breast milk is catabolized to glucose + galactose.

It is exceedingly HY that **galactitol** causes the cataracts. [Aldose reductase](#) turns galactose into galactitol.

USMLE questions are obsessed with **aldose reductase** being the cause of cataracts in galactose disorders. Aldose reductase converts galactose to **galactitol**, which, like sorbitol in diabetes, becomes trapped in the lens and causes damage.

There's also one last really important factoid about classic galactosemia:

***E. coli* sepsis in a neonate is associated with classic galactosemia.**

Why? Who knows. We can speculate it has something to do with *E. coli* being a gram (-) lactose-fermenting rod, and lactose = glucose + galactose. In addition, infections with Group B Strep (*S. agalactiae*), *E. coli*, and *Listeria* are common in neonates.

—

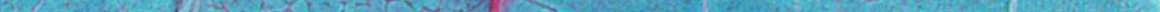
1. What is the enzyme responsible for cataracts in galactose disorders?

- ☐ Galactokinase
- ☐ Galactose-1-phosphate uridylyltransferase (GALT)
- ☐ Aldose reductase

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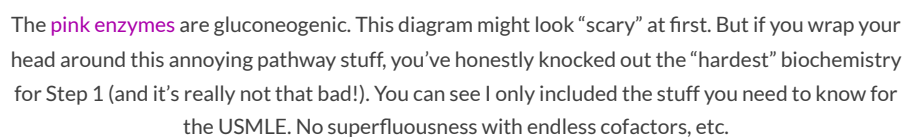
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Gluconeogenesis

GLUCONEOGENESIS



1) Pyruvate carboxylase

- Converts pyruvate → OAA
- **Biotin (vitamin B7)-dependent enzyme.**
- As I talk about in [this post](#), **acetyl-coA is a (+) regulator of pyruvate carboxylase**, which is why carnitine or acyl-CoA (not acetyl-CoA) dehydrogenase deficiency leads to hypoketotic hypoglycemia.

2) PEP carboxykinase

- Converts OAA back to PEP. Then PEP can work its way back up to glucose.

3) Fructose-1,6-bisphosphatase

- Rate-limiting enzyme of gluconeogenesis.

4) Glucose-6-phosphatase

- Enables G6P to go back to glucose.
- Deficiency causes [von Gierke disease](#) (glycogen storage disease type I).
- G6Pase **is not found in skeletal muscle**, which is why skeletal muscle does not partake in gluconeogenesis.
- G6Pase is found predominantly in the liver.

—

So far so good?

Now we can look at another way to get back to glucose:

Whereas even-chain FAs only yield 2-carbon acetyl-CoAs, odd-chain FAs are terminally catabolized to a 3-carbon molecule called propionyl-CoA. (If you want more detail on this, open [this post](#) in a separate tab).

Propionyl-CoA carboxylase converts propionyl-CoA → methylmalonyl-CoA via biotin (B7).

Methylmalonyl-CoA mutase then converts methylmalonyl-CoA to succinyl-CoA in the TCA cycle. **This reaction requires vitamin B12.**

Same as how vitamins B6 and B7 are involved in decarboxylase and carboxylase reactions, respectively, vitamin B12 is involved in **isomerase** reactions. Methylmalonyl-CoA mutase is a type of isomerase.

Buildup of methylmalonyl-CoA in B12 deficiency is what leads to myelin toxicity and **subacute combined degeneration**, which is the name of the neurological condition seen in B12 deficiency.

The involved tracts are the corticospinal tract, dorsal columns, and spinocerebellar tract.

Sounds pedantic, but trust me, they ask specifically for those three tracts.

I find an easy way to remember which three are affected is to start by saying, "The spinothalamic tract is not involved."

So that's the highest-yield information regarding gluconeogenesis for Step 1. The aim of this post wasn't to give you a superfluous and unabridged biochemistry lecture regarding bullshit detail that will never show up. If you know the content on this page, you're solid. You might also want to take a look at this HY post on [glycogen metabolism](#).

—

1. Which of the following are gluconeogenic enzymes? (Select all that apply)

- ☐ Pyruvate dehydrogenase
- ☐ Pyruvate carboxylase
- ☐ PEP carboxykinase
- ☐ Pyruvate kinase

- ☐ Lactate dehydrogenase
- ☐ Phosphofructokinase-1
- ☐ Fructose-1,6-bisphosphatase
- ☐ Glucokinase
- ☐ Hexokinase
- ☐ Glucose-6-phosphate dehydrogenase
- ☐ Glucose-6-phosphatase
- ☐ Propionyl-CoA carboxylase
- ☐ Propionyl-CoA decarboxylase
- ☐ Methylmalonyl-CoA isomerase
- ☐ Methylmalonyl-CoA mutase

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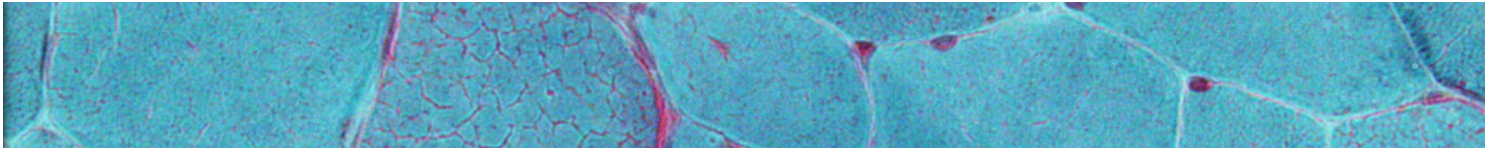
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HY USMLE Q #940 – Biochemistry

January 1, 2024



BIOCHEMISTRY

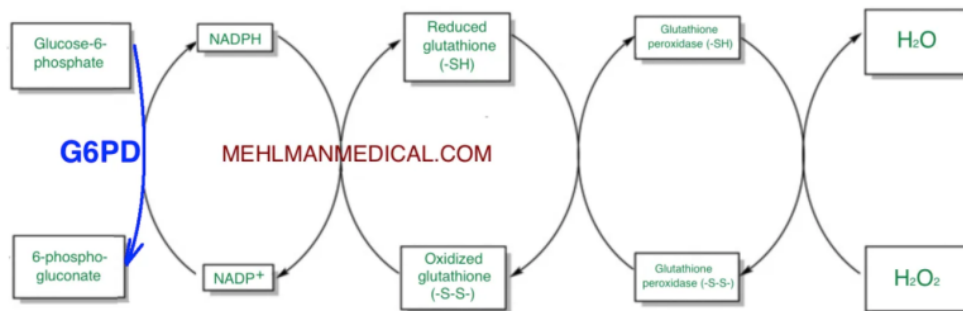
Glucose-6-phosphate dehydrogenase (G6PD) deficiency

by MEHLMANMEDICAL

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Before even telling you what G6PD is or why it's significant, you need to know this:

A USMLE question writer's obsession: G6PD deficiency is X-linked recessive.

Ok cool. Now that that's out of the way, the reason the USMLE gives a fuck about G6PD is because it's used to generate **NADPH**.

Why is NADPH important? Because its production ultimately leads to the mopping up of free radicals and the neutralizing of oxidizing agents and H₂O₂.

Presence of G6PD → means NADPH production → ↑ protection against oxidizing agents + H₂O₂

Adding an extra piece of info, NADPH helps convert oxidized glutathione into reduced glutathione. The latter is a reducing agent that neutralizes oxidizing agents.

Oxidizing agents = damage DNA = bad

Reducing agents = neutralize oxidizing agents → therefore good

Presence of G6PD → production of NADPH → more reduced glutathione → more (H₂O₂ → H₂O)

In turn, G6PD deficiency can lead to hemolysis secondary to oxidative stress.

Sulfa drugs (e.g., furosemide, sulfonamides, sulfonylureas) are notorious for causing hemolysis in G6PD.

Questions classically mention an African-American boy with decreased hematocrit after receiving a drug (e.g., **dapsone**, **primaquine**, **sulfonamides**).

But hemolysis can also occur with consumption of **fava beans** (favism).

Questions also love to you to know **bite cells** and **Heinz bodies** are characteristic of G6PD deficiency.

Heinz bodies = denatured/oxidized hemoglobin inside RBCs

Bite cells (degmacytes) = RBCs with tiny, semicircular pieces missing that are formed when the spleen removes the Heinz body but allows the rest of the RBC to remain in the circulation. These RBCs nevertheless have decreased lifespan.

The reduced lifespan of a bite cell RBC = $\uparrow$ RBC turnover = $\uparrow$ resistance to malaria.

G6PD deficiency and sickle cell trait/disease both confer resistance to malaria because shortened RBC lifespan $\rightarrow$ impedence of malaria lifecycle

The last factoid:

Two most common causes of hemolytic anemia secondary to enzyme deficiency: 1) **G6PD deficiency**; 2) **Pyruvate kinase deficiency**

Pyruvate kinase is the last enzyme of glycolysis (PEP $\rightarrow$ pyruvate). ATP is produced in this step.

Pyruvate kinase deficiency $\rightarrow$ decreased ATP $\rightarrow$ decreased RBC Na/K ATPase activity $\rightarrow$ Na builds up inside RBC $\rightarrow$ RBC swelling + lysis.

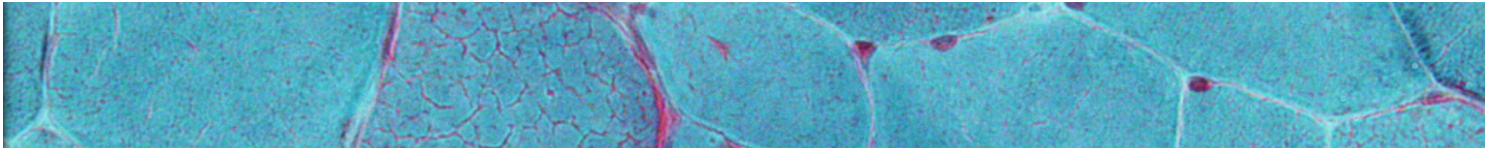
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1. What is the inheritance pattern of G6PD deficiency?

- ☐ AR
- ☐ AD
- ☐ XR
- ☐ XD

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Glycogen storage diseases

by MEHLMANMEDICAL

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These are all autosomal recessive. I will not talk about them in order for reasons I'll discuss.

For starters, I'll group the following two together because the USMLE likes you to differentiate them:

Von Gierke disease (type I) = ↓ glucose-6-phosphatase (G6Pase deficiency; **NOT G6PD deficiency**)

Cori disease (type III) = ↓ α-1,6-glucosidase (debranching enzyme)

Von Gierke is the most severe glycogen storage disorder. There's hepatic steatosis with hepatomegaly, very severe fasting hypoglycemia and **increased blood lactate**.

The increased blood lactate is the most important part.

In contrast to von Gierke disease, Cori disease **DOES NOT** have increased blood lactate. That is the highest yield point you need to know.

Seemingly "severe" presentation in a young child with lactic acidosis → von Gierke disease

Seemingly "not that severe" presentation in a child where they specifically say **no** lactic acidosis → Cori disease

Likewise:

Bicarbonate (HCO_3^-) in the normal range (22-28)? Yes, in normal range → no lactic acidosis → Cori disease

Bicarbonate (HCO_3^-) in the normal range (22-28)? No, bicarb is low (<22) → due to lactic acidosis → von Gierke disease

With von Gierke disease, **patients need to avoid both fructose and galactose** because consumption of either will lead to buildup of glycolytic intermediates and depletion of available hepatic phosphate.

Therefore:

Do glucose levels rise after giving fructose? Yes, glucose levels rise → intact gluconeogenesis → Cori

Do glucose levels rise after giving fructose? No, glucose levels don't rise → gluconeogenesis impaired due to ↓ G6Pase → von Gierke

Pompe disease (type II) = ↓ lysosomal α -1,4-glucosidase (acid maltase)

Literally (and I'm not joking), the only presenting feature you need to know about Pompe is that it causes cardiomyopathy. Essentially, if you get a glycogen storage disease question and they mention anything about the heart in a young child, the answer is Pompe.

Heart problems in a glycogen storage disease question = Pompe disease

Pompe is the only glycogen storage disease where the deficient enzyme is notably located in the **lysosome**. For the others, choose **cytosol**. By all means, yes, the lysosome is inside the cytosol, but I'm just making a point that for whatever reason the USMLE is known to ask this weird point of differentiation.

McArdle disease (type V) = ↓ myophosphorylase (muscle glycogen phosphorylase)

Pretty much 100% of the time, the vignette they'll give you is a late-teen or young adult who **performs some form of intense exercise** (e.g., shoveling snow, sprinting) and then gets **painful muscle cramps and red/dark urine**.

If they ever ask you about an electrolyte abnormality in this situation, the answer is hyperkalemia secondary to **rhabdomyolysis**. It's the myoglobin in the urine that makes it dark.

Dipstick of the urine will be (+) for blood, but urinalysis will reveal no RBCs. The dipstick is merely detecting the myoglobin.

Myoglobinuria causes a false (+) for blood on dipstick. Therefore, e.g., ++ blood on dipstick, but 0-1 RBCs per high-power field on light microscopy (negative RBCs), think rhabdo.

If they ask you about the type of renal injury secondary to McArdle, **the answer is acute tubular necrosis** secondary to the nephrotoxic effects of myoglobin.

Acute tubular necrosis = **muddy brown, granular casts** on urinalysis. These are sloughed PCT tubular cells, **not** RBCs.

ATN is a type of intra-renal failure with a BUN/Cr <20, a FE_{Na} >1%, and ↓ urine osmolality.

The USMLE doesn't ask about glycogen storage disease type IV (Andersen disease) for whatever reason.

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1. What is the enzyme deficiency in von Gierke disease?

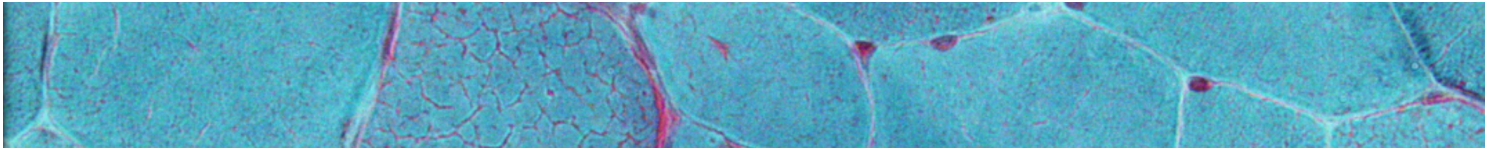
- ☐ Alpha-1-4-glucosidase
- ☐ Alpha-1-6-glucosidase
- ☐ Glucose-6-phosphatase
- ☐ Glucose-1-phosphatase
- ☐ Glucose-6-phosphate dehydrogenase
- ☐ Myophosphorylase (muscle glycogen phosphorylase)

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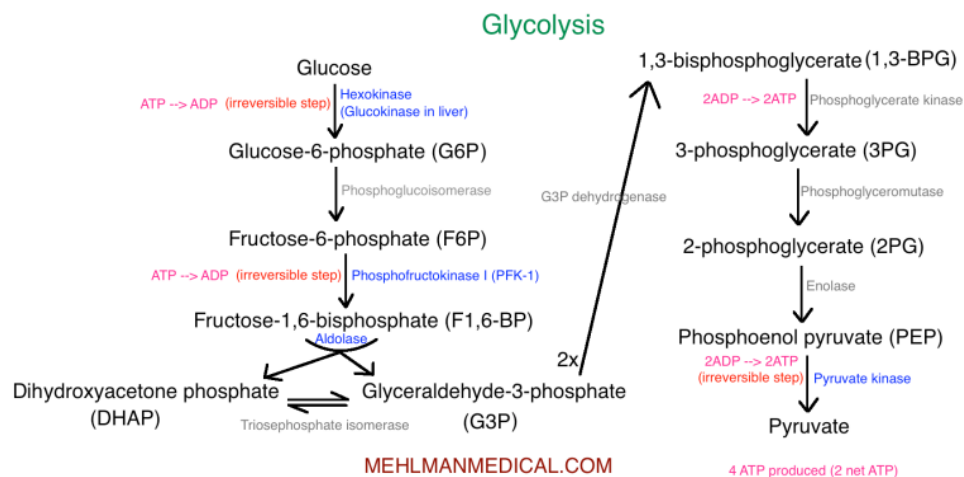
Glycolysis

by MEHLMANMEDICAL

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Blue enzymes are important. Grey ones you don't need to know but I've written for the sake of completion. To memorize the irreversible enzymes, just remember "1, 3, 9," which corresponds to the step #s.

The following is not bullshit superfluousness and is literally what you need to know for Step1 for glycolysis:

The irreversible steps are:

1. Glucose → G6P (hexokinase/glucokinase)
2. F6P → F1,6-BP (PFK-1)
3. PEP → pyruvate (pyruvate kinase)

Pyruvate kinase is a deceitful name because PEP loses a P_i . That's the only exception on Step1.

Some molecular regulators of glycolysis:

ATP, NADH, citrate, and alanine inhibit glycolysis.

In contrast, AMP and ADP stimulate glycolysis.

Phosphofructokinase 1 (PFK1) is the rate-limiting enzyme, not hexokinase/glucokinase.

Hexokinase is the first enzyme of glycolysis everywhere except for the liver and β -islet cells of the pancreas. In the liver + β -cells, glucokinase is the first enzyme.

The USMLE is obsessed with testing hexokinase vs glucokinase.

Enzyme	Where	Km	Vmax	Stimulated by insulin?
Hexokinase	Mostly ubiquitous	↓	↓	No
Glucokinase	Liver + β -islets of pancreas	↑	↑	Yes

Hexokinase has a higher affinity for glucose (↓ Km) but gets saturated quickly (↓ Vmax).

In contrast, glucokinase has a lower affinity for glucose (↑ Km) but can tolerate high amounts of it (↑ Vmax).

This makes sense because most of the time we want glucose to be taken up peripherally, not by the liver for storage. Therefore the liver *should have* lower affinity for it.

When glucose is high, we want the liver to start storing it as glycogen. In this case, high glucose means high insulin, which then stimulates glucokinase in the liver to start buffering the excess load.

Insulin does **NOT** stimulate hexokinase. **Only glucokinase is stimulated by insulin.**

Fasting state → insulin lower → ↓ stimulation of glucokinase in the liver → hexokinase takes up glucose peripherally

Fed state → insulin higher → ↑ stimulation of glucokinase in the liver → liver buffers excess blood glucose → **insulin dephosphorylates and activates glycogen synthase → excess glucose stored as glycogen (elaboration in this module)**

Holy cow:

Although insulin drives glucose into cells by upregulating GLUT4 recruitment to adipocyte and skeletal muscle cell membranes, the dephosphorylation and activation of glycogen synthase + the activation of hepatic glucokinase, perpetuated by insulin, decreases/buffers blood glucose levels by creating additional G6P and shuttling it to G1P for glycogenesis.

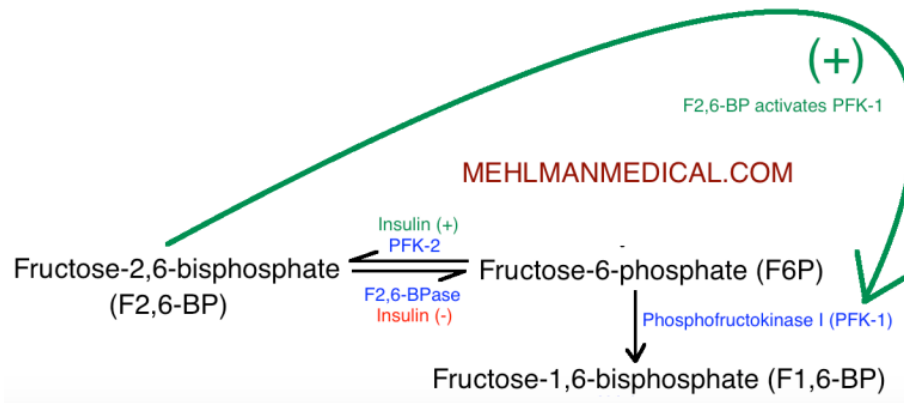
In the second half of glycolysis, normally, 1,3-bisphosphoglycerate → 3-phosphoglycerate. **However, RBCs have bisphosphoglycerate mutase that allows for them to convert 1,3-bisphosphoglycerate → 2,3-bisphosphoglycerate (2,3-BPG, or 2,3-DPG) → 3-phosphoglycerate.**



2,3-BPG (2,3-DPG) decreases the affinity of oxygen for deoxyhemoglobin (i.e., shifts the Hb-O₂ dissociation curve to the right).

The bottom line is that if they ask you about what type of cell has an enzyme called **bisphosphoglycerate mutase**, the answer is RBC, because this enzyme is what creates 2,3-BPG from 1,3-BPG.

Normally, $F6P \rightarrow F1,6\text{-BP}$ via PFK-1. When the insulin/glucagon ratio is $\uparrow$ (i.e., in the fed state), some F6P is instead shunted, via PFK-2, to F $\underline{2}$,6-BP.



F $\underline{2}$,6-BP then acts as a (+) allosteric regulator of PFK-1, the rate-limiting enzyme of glycolysis, to further stimulate $F6P \rightarrow F1,6\text{-BP}$.

In other words, F $\underline{2}$,6-BP is what stimulates the rate-limiting enzyme of glycolysis.

In contrast, when the insulin/glucagon ratio is $\downarrow$ (i.e., in the fasting state), any available F $\underline{2}$,6-BP is shunted back to F6P, via F2,6-BPase, and the $F6P \rightarrow F1,6\text{-BP}$ step is **not** stimulated.

—

(If the following comes off confusing, open [this post](#) in a separate tab.)

PFK2 is **dephosphorylated** and **activated** by $\uparrow$ insulin/glucagon.

F2,6-BPase is **dephosphorylated** and **deactivated** by $\uparrow$ insulin/glucagon.

PFK2 is **phosphorylated** and **deactivated** by $\downarrow$ insulin/glucagon.

F2,6-BPase is **phosphorylated** and **activated** by $\downarrow$ insulin/glucagon.

—

The final product of glycolysis is 2x pyruvate, from one glucose.

4 ATP are produced. But 2 are consumed. So 2 net ATP are produced.

—

Pyruvate dehydrogenase + B1 (and B2, 3, 5, and lipoic acid): pyruvate $\rightarrow$ acetyl-CoA

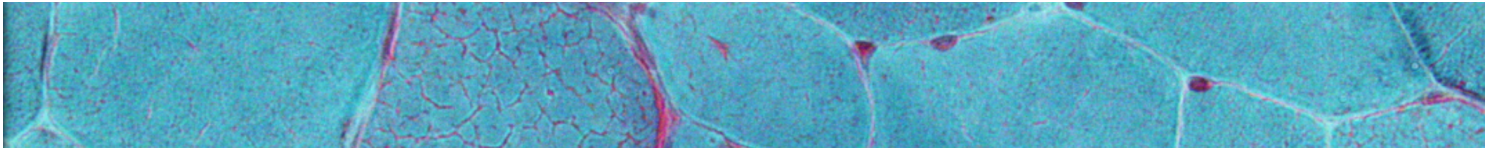
Pyruvate carboxylase + B7: pyruvate $\rightarrow$ OAA (for gluconeogenesis, not glycolysis)

Lactate dehydrogenase: pyruvate + NADH $\leftrightarrow$ lactate + NAD $^{+}$

Alanine transaminase (ALT) + B6: pyruvate + glutamate $\leftrightarrow$ alanine + α -KG

—

1. What are the three irreversible steps of glycolysis + their enzyme names? (6 points)



BIOCHEMISTRY

Hartnup disease and Fanconi syndrome

by MEHLMANMEDICAL

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Hartnup disease

Characterized by a **decreased ability to reabsorb non-polar amino acids (notably tryptophan)** in the PCT.

Why does the USMLE give a fuck?

Because tryptophan is a precursor of both serotonin and niacin, so urinary loss of tryptophan due to Hartnup disease or increased utilization of it to make serotonin in carcinoid syndrome **leads to niacin deficiency**.

Hartnup disease → ↓ tryptophan → ↓ niacin (B3) → pellagra

↑ serotonin production (carcinoid syndrome) → ↓ tryptophan → ↓ niacin → pellagra

You might get a vignette of pellagra (dementia, dermatitis, diarrhea) where the answer is “impaired tubular reabsorption of dietary amino acid.”

Fanconi syndrome

Tryptophan is a neutral amino acid. So if they tell you that a patient has tryptophan *and charged amino acids* in the urine (e.g., proline, hydroxyproline, arginine), **think Fanconi syndrome instead of Hartnup disease**.

Fanconi syndrome is characterized by a **more non-selective** inability to reabsorb amino acids from the urine (as well as glucose, phosphate and bicarbonate).

The USMLE will give you a chart with “decreased” or “unchanged” combinations with respect to PCT reabsorption of various solutes. For Fanconi syndrome, you need to know for amino acids, glucose, bicarb, and phosphate, **reabsorption is decreased for all of them**.

Fanconi syndrome	Amino acids	Glucose	Bicarb	Phosphate
PCT reabsorption (↓ or unchanged)	↓	↓	↓	↓

Because there's ↓ bicarb reabsorption in Fanconi syndrome, it is a known cause of **renal tubular acidosis type II (RTA II)**.

Fanconi syndrome can be caused by consumption of **expired tetracyclines**.

Don't confuse Fanconi syndrome with **Fanconi anemia**. The latter is a congenital aplastic anemia, where the patient also has absent or hypoplastic thumbs or radii.

Then when you go off thinking you're cool that you know Fanconi syndrome has the latter detail, **Diamond-Blackfan anemia** is a pure RBC aplasia characterized by **triphalangeal thumbs**, not absent/hypoplastic ones as in Fanconi syndrome. UWorld for Step 3 actually has a question comparing these two (random I know).

1. Young boy with triphalangeal thumbs. Which of the following are correct? (Select two; two points)

- ☐ Fanconi anemia
- ☐ Fanconi syndrome
- ☐ Diamond-Blackfan anemia
- ☐ Decreased RBCs only
- ☐ RBCs, WBCs, platelets all decreased

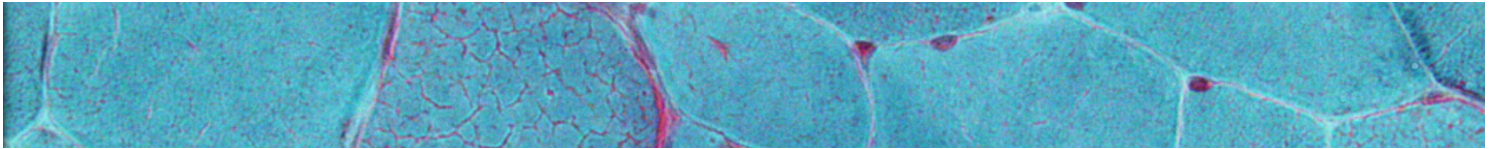
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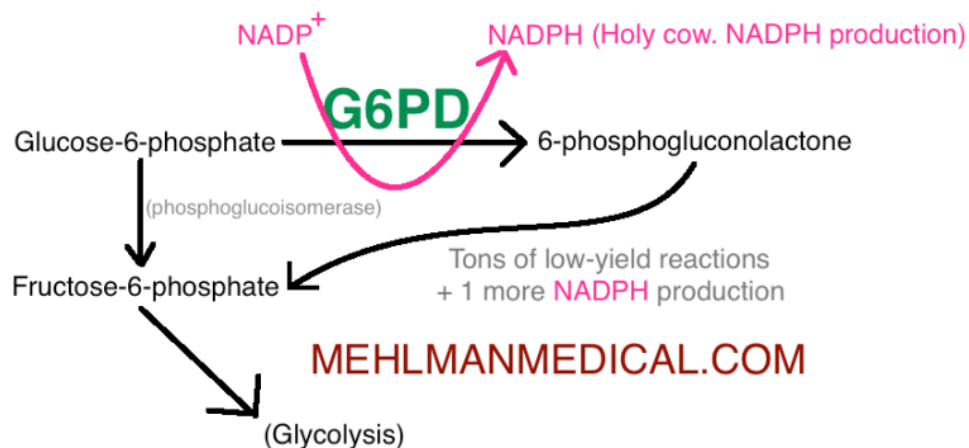
Hexose monophosphate (HMP) shunt

by MEHLMANMEDICAL

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In the HMP shunt, glucose-6-phosphate, which normally proceeds through glycolysis, can instead be shunted through this side-pathway to produce numerous intermediates and **NADPH**.

The USMLE gives a fuck about NADPH because this molecule plays an important role in the **respiratory burst** and the regeneration of **reduced glutathione**. Reduced glutathione is protective against oxidizing agents and helps keep RBC membranes stable.

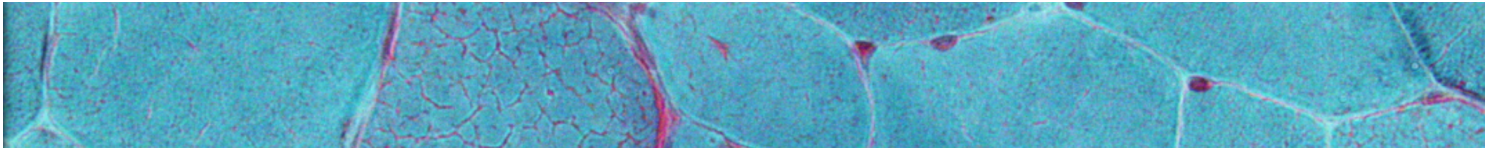
The **rate-limiting enzyme** that allows for this shunting to occur is **glucose-6-phosphate dehydrogenase (G6PD)**.

Therefore, G6PD deficiency $\rightarrow$ $\downarrow$ NADPH $\rightarrow$ hemolysis in the event of stressors such as **drugs, fava beans, DKA, infection, trauma**.

Finally, **transketolase** is used to recycle excess HMP intermediates back to fructose-6-phosphate in glycolysis. This enzyme is thiamine-dependent.

If someone is administered thiamine in the setting of suspected deficiency and they tell you transketolase activity increases $<5\%$, it means the patient did not have thiamine deficiency. If enzyme activity increases $>15\%$, that means there was severe deficiency.

1. What molecule is crucially made as a result of the HMP shunt?



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Homocystinuria

by MEHLMANMEDICAL

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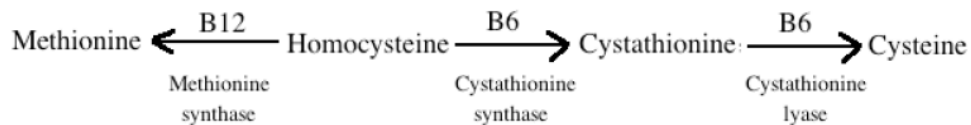
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Homocystinuria is an AR disease characterized by a buildup of homocysteine due to **deficiency of cystathionine synthase**.

Homocystine = 2 homocysteine molecules bound together by a disulfide bond.

Each homocysteine has an -SH (thiol group), and oxidation makes them join together to form -S-S-.



The patient in homocystinuria will present as a school-age child with **Marfanoid body habitus and thrombotic events**.

The classic USMLE vignette is a 12-year-old girl who is **tall and lanky**, possibly with scoliosis or kyphosis, who experiences a **lens dislocation** while at school. They'll try to trick you into thinking it's Marfan syndrome, but then they'll mention something about a **thrombotic event or myocardial infarction**.

Weird, but homocystinuria is also associated with **early-onset osteoporosis**.

If you get a question that sounds like Marfan syndrome in a school-age child, **but then they say anything about thrombosis or MI, the answer is homocystinuria**.

Some resources might mention that Marfan syndrome patients have upward dislocation of the lens, whereas in homocystinuria, the lens is dislocated downward + inward, but I can tell you that detail is meaningless for the Step and a question would never hinge on it. I only mention this here because some people might otherwise think that's an important detail I've left out.

If they ask you about which amino acid is essential in homocystinuria, the answer is cysteine because it is deficient. In contrast, methionine is in excess.

The USMLE likes to assess vitamin B6 as an ancillary Tx for homocystinuria.

If they ask you about what could help a homocystinuria patient, but cysteine isn't an answer, **look for pyridoxine as an answer choice (vitamin B6)**, since it is a cofactor for cystathionine synthase.

1. 22 yr-old male. 6' 5". High-arched palate. Arachnodactyly. His mother, also tall, had a tumor removed from her neck however many years ago. Diagnosis?

- ☐ Homocystinuria
- ☐ Marfan syndrome
- ☐ Multiple endocrine neoplasia 1
- ☐ Multiple endocrine neoplasia 2A
- ☐ Multiple endocrine neoplasia 2B

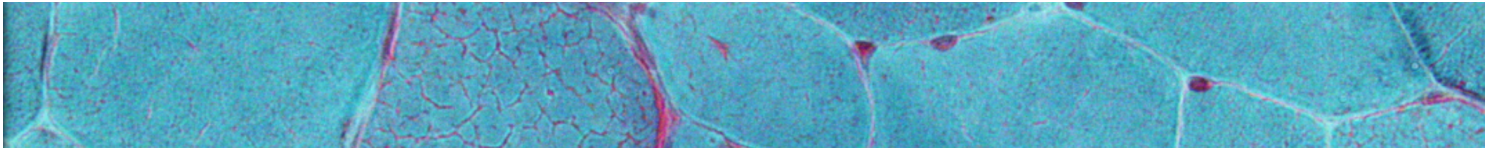
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Krebs (TCA) cycle

by MEHLMANMEDICAL

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Cutting to the chase. Key factoids:

Pyruvate dehydrogenase (PDH) is thiamine-dependent, and absence or dysfunction of this enzyme causes **severe lactic acidosis and increased serum alanine**. Why?

Buildup of **pyruvate** means increased shunting to:

Lactate (pyruvate + NADH ↔ lactate + NAD⁺)

Alanine (pyruvate + glutamate ↔ α-ketoglutarate + alanine)

Tx with ↑ dietary ketogenic nutrients (e.g. leucine, lysine and healthy oils; all → acetyl-CoA, not pyruvate).

USMLE says: a patient has **severe acidosis** and ↑↑ **serum alanine**. **The answer is pyruvate dehydrogenase deficiency.**

Arsenic inhibits PDH.

Arsenic poisoning causes **garlic-smelling breath**.

Isocitrate dehydrogenase is the rate-limiting enzyme of the TCA cycle.

The USMLE is occasionally known to test rate-limiting enzymes. It's a weird/obscure enzyme name, but the TCA cycle is so high-yield for pathway biochemistry that you should know this enzyme regardless.

α-ketoglutarate dehydrogenase, like PDH, is thiamine-dependent.

The four thiamine-dependent enzymes are pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, branched-chain ketoacid dehydrogenase, and transketolase.

Pyruvate, instead of going to acetyl-CoA via PDH and B1, can also go to OAA via pyruvate carboxylase and vitamin B7 (biotin).

Pyruvate dehydrogenase (anabolic enzyme) = B1-dependent = takes pyruvate into the TCA cycle

Pyruvate carboxylase (catabolic enzyme) = B7-dependent = takes pyruvate backwards to glucose (via OAA in order to get to PEP)

The $\uparrow$ NADH/NAD⁺ ratio caused by alcohol increases OAA $\rightarrow$ malate, thereby depleting OAA to be shuttled to PEP for gluconeogenesis.

Fasting hypoglycemia in alcoholism is partially due to impaired gluconeogenesis because of shunting of OAA to malate.

Succinyl-CoA (of TCA cycle) can be produced from methylmalonyl-CoA (not in TCA cycle) via vitamin B12. **It is inhibition of this step in B12-deficiency that is responsible for neurologic dysfunction** and myelin sheath abnormalities.

Impaired methylmalonyl-CoA $\rightarrow$ succinyl-CoA is responsible for the neurologic dysfunction in B12-deficiency.

Succinyl-CoA $\rightarrow$ succinate is the step where **GTP** is produced. **Succinate $\rightarrow$ fumarate** is the step where **FADH₂** is produced and **vitamin B2** is a cofactor.

The only thing you need to know about vitamin B2 for the USMLE (and in life essentially) is that it's called riboflavin and is used in the above reaction.

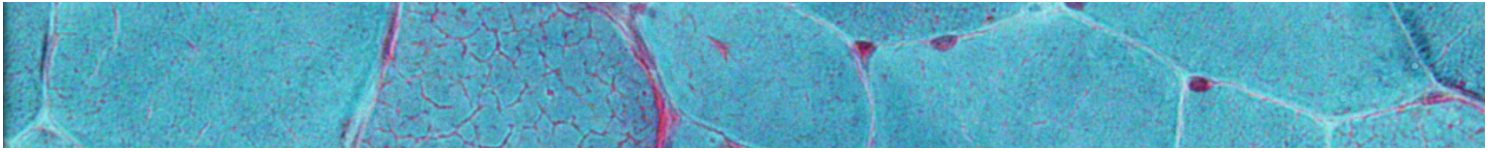
The TCA cycle produces lots of NADH and a molecule of FADH₂, which are ultimately used to drive protons into the intermembrane space of the mitochondria in order to generate ATP. The HY factoids for this process (electron transport chain) are discussed [here](#).

—

1. Severe lactic acidosis + increased serum alanine. Diagnosis?

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Kwashiorkor vs Marasmus vs Cretinism

by MEHLMANMEDICAL

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The USMLE will sometimes ask tricky questions where the distinction between these three conditions may seem equivocal. So I'll highlight the highest yield points:

Marasmus is **total-calorie deficiency** presenting as diffuse wasting.



Marasmus with diffuse wasting; no pot-belly

In contrast, kwashiorkor is an overwhelming **protein malnutrition**. Even if total calorie intake is inadequate (it often is), of the calories that are consumed, the lack of protein (e.g., from nothing but ongoing rice consumption), the result is hypoalbuminemia, decreased intravascular oncotic pressure, and, ultimately, **ascites**.



Kwashiorkor – notable ascites (pot-belly)

So far so good. Not hard.

Now we introduce **cretinism**, which is **congenital hypothyroidism**.



Cretinism. Can outwardly appear similar to kwashiorkor

The USMLE will try to trick you because cretinism can also present with protruding abdomen.

On the USMLE, cretinism will always present with severe mental impairment, whereas kwashiorkor frequently will not. Cretinism will also frequently present with **large tongue** and **impaired linear bone growth**. This is because thyroid hormone is necessary for myelin and skeletal development.

It should also be noted that, worldwide, the most common cause of hypothyroidism is **iodine deficiency**. But in **western countries**, the most common cause is **Hashimoto thyroiditis**.

Some USMLE distinctions:

Protruding abdomen alone mentioned.

Is there any mental impairment? **No**. → Kwashiorkor

Is there any mental impairment? **Yes, there's mental impairment**. → Cretinism

If the question is relatively vague but presents what seems like a malnourished infant, if they go out of their way to mention that **the bones aren't developing well**, cretinism is the answer because thyroid hormone is necessary for bone development, as we've mentioned.

Also, if the vignette gives you a patient with kwashiorkor and asks for the amino acid that will best treat it, **the answer usually leucine, lysine, or tryptophan**.

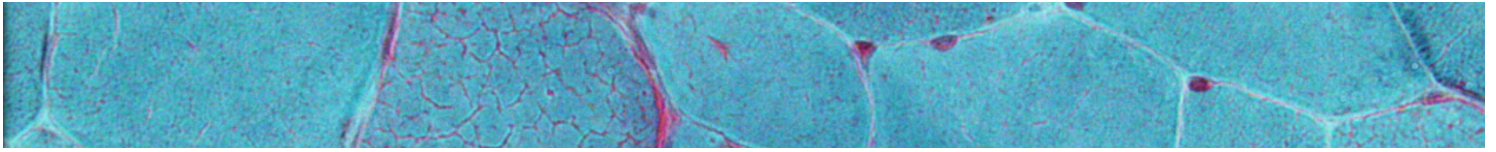
Technically there are nine essential amino acids (histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine) and six conditionally essential amino acids (arginine, cysteine, glutamine, glycine, proline, tyrosine). **You do *not* need to memorize these for the USMLE**.

So why lysine or tryptophan? Yeah I know, weird. But let's just run with it. It's what the USMLE wants and they've shown up in questions as the answer.

The heel-prick test done at birth, where a drop of blood is taken from the neonate to be screened for congenital hypothyroidism, **PKU**, and galactose disorders, among others, is performed notably to detect as early as possible preventable causes of mental retardation.

1. Child with protruding abdomen. There is no mental impairment. Diagnosis?

- ☐ Marasmus
- ☐ Kwashiorkor
- ☐ Cretinism



BIOCHEMISTRY

Lactase deficiency (lactose intolerance)

by MEHLMANMEDICAL

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Lactase deficiency

Lactase breaks down lactose into glucose + galactose. It is a brush border disaccharidase.

Your disaccharides:

Lactose = glucose + galactose

Maltose = 2 x glucose

Sucrose = glucose + fructose

If the question asks you where the enzyme is located, it is **on the surface of the enterocytes**, predominantly in the jejunum.

The brush border location of lactase is exceedingly HY.

Intestinal biopsy shows **NORMAL-appearing villi**, or “**benign mucosa**.” There is **nothing** wrong with the villi appearance-wise in lactase deficiency.

In contrast, **Celiac disease**, which is gluten intolerance, **has blunting of the villi** on biopsy.

Normal biopsy → lactase deficiency

Flattened villi → Celiac disease

Not rocket science. But for some reason if people get asked about the biopsy finding in lactase deficiency they're often deer in the headlights.

A super-HY USMLE pearl is that **gastroenteritis can lead to transient (secondary) lactose intolerance** due to shedding/inflammation of intestinal epithelium, which is where the disaccharidase resides.

This is most notably due to **rotavirus infection** in pediatrics.

The classic USMLE question will mention a kid with recent watery diarrhea (rotavirus) who, after having recovered, presents with new-onset **osmotic diarrhea, bloating, and cramps** following consumption of dairy products. **This is self-limited lactase deficiency.**

Annoying, but the USMLE sometimes refers to lactose (not lactase) as **galactosyl β -1,4-glucose**.

Sometimes the question will mention in the stem that a patient has been having diarrhea (they won't mention dairy products), and that **stool demonstrates $\downarrow$ pH and breath shows $\uparrow$ hydrogen content**. This is important because hydrogen breath test and stool pH are diagnostic tests.

—

1. How do you diagnose lactase deficiency? (two ways; two points)

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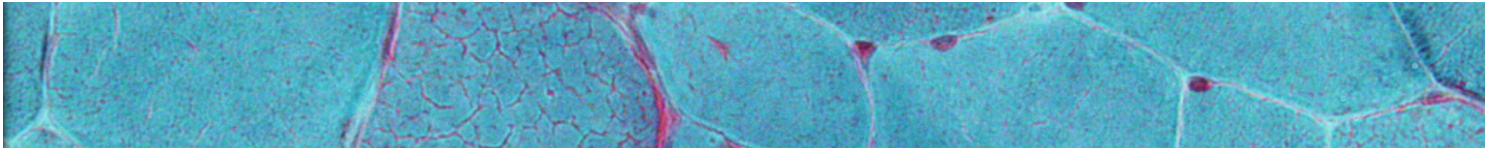


HY USMLE Q #940 – Biochemistry

January 1, 2024



≡ MAIN MENU



BIOCHEMISTRY

Lactulose vs Neomycin

by MEHLMANMEDICAL

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You're probably wondering why I wrote a post about two seemingly weird drugs. Yeah I know, weird. By all means, I could have not mentioned the following HY points at all, but I figured it's better to at least get them out there.

If you're ever asked about the treatment of hyperammonemia on the USMLE, it will be one of two drugs: **lactulose** or **neomycin**.

Lactulose increases gut excretion of ammonia by enabling its conversion to ammonium. Since we are not able to break it down, gut bacteria are able to ferment it. This fermentation leads to acid production, so more intraluminal NH_3 is converted to NH_4^+ . Since charged entities are not absorbed as readily, excretion is increased. Pretty straightforward.

The USMLE also wants you to know that **neomycin**, an aminoglycoside, kills urease (+) organisms, therefore decreasing NH_3 production. If they ever ask you about an antibiotic that can treat hyperammonemia, **look for neomycin as an answer**. This drug is floating around on the newer NBMEs as well.

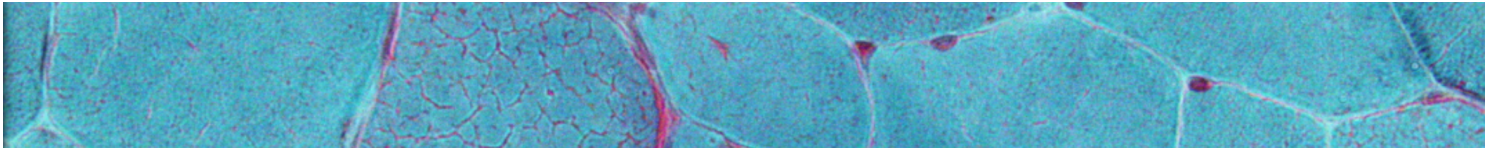
That's literally it. Two weird HY drugs out of the way.

Some texts might mention benzoate or phenylbutyrate as drugs that bind amino acids in the bloodstream and increase their excretion before their amine groups can be liberated via catabolism, but I'd be wildly surprised if either of these ever shows up on a real exam. The only reason I'm mentioning them here is because someone who's pedantic might otherwise say, "Yeah but Michael, you didn't mention benzoate or phenylbutyrate." So there you go. I did. But once again, they're not HY. Just know lactulose and neomycin.

—

1. How does lactulose work in terms of decreasing ammonia in the blood?

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BIOCHEMISTRY

Lysosomal storage diseases

by MEHLMANMEDICAL

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You will get asked a lysosomal storage disease question on your real USMLE. Memorizing the respective enzyme deficiencies and accumulated substrates is mandatory if you want anything 240s or higher. Gaucher could even be considered 220s truthfully.

For starters, the USMLE obsesses over which of these conditions are autosomal recessive (AR) vs X-linked recessive (XR).

Make a point to remember that Fabry disease and Hunter syndrome are both XR. The rest are AR.

For whatever magical reason, the USMLE cares that you know Fabry and Hunter are XR.

Fabry disease = ↓ α-galactosidase A enzyme = ↑ ceramide trihexoside substrate = XR

The classic presentation on the Step1 is **burning pain in the extremities** in the setting of **kidney or heart problems**. Fairly straightforward.

Sometimes they'll also mention **red, non-blanching macules/papules between the umbilicus and knees (angiokeratomas)**. If they mention any of those findings within the context of a lysosomal storage disease → Fabry disease.

Gaucher disease = ↓ glucocerebrosidase (glucosylceramidase) = ↑ glucocerebroside (glucosylceramide) = AR

The one feature that sets Gaucher apart from the other lysosomal storage diseases is that it causes **aseptic necrosis of the femur with bone crisis**. If they mention a lysosomal storage disease and then any type of presentation suggesting **bone problems**, Gaucher is the answer.

The USMLE also loves to mention that **macrophages are found to have a "crinkly" or "crumpled tissue paper" appearance**. Hepatosplenomegaly, vertebral collapse, anemia, thrombocytopenia and bone infarction are traditional findings.

How do you treat Gaucher disease? **Imiglucerase** = recombinant glucocerebrosidase. Not hard, but was asked in a question somewhere.

The following two I'm grouping together for a reason:

Tay-Sach disease = ↓ hexosaminidase A = ↑ GM₂ ganglioside = AR

Niemann-Pick disease = ↓ sphingomyelinase = ↑ sphingomyelin = AR

Cherry red spot on the macula is seen in **BOTH** Tay-Sach and Niemann-Pick disease on USMLE Step1. But **only** Niemann-Pick will have hepatosplenomegaly. The way to remember this is: Niemann-Pick is a longer name than Tay-Sach, and hepatosplenomegaly is a long word, so that's the one that has HSM. Simple yet revolutionary, I know.

So in the event that there's an infant with neuronal degeneration + a cherry-red macula:

Is hepatosplenomegaly present? No, there's no HSM → Tay-Sach disease

Is hepatosplenomegaly present? Yes, HSM present → Niemann-Pick disease

Occasionally, they will also mention **foam cells**, which are lipid-laden macrophages.

"Foam" and "Niemann" both have an "m".

Metachromatic leukodystrophy = ↓ arylsulfatase A = ↑ cerebroside sulfate = AR

Mention of **color** change or staining in a lysosomal storage disease question = **metachromatic** leukodystrophy.

This condition tends to present with overall CNS and PNS demyelination. The vignette may also mention ataxia. The USMLE tends to mention that an infant with neurological dysfunction was found to have **macrophages that appeared brown when stained with toluidine blue**. Or an infant with neurological dysfunction was found to have **macrophages that appeared purple when stained with cresyl violet**. Apparently cerebroside sulfate can appear these colors when stained. Not HY, but I mention this disease anyway for the sake of completion and because it inevitably shows up in Qbanks.

Krabbe disease ↓ galactocerebrosidase (galactosylceramidase) = ↑ galactocerebroside (galactosylceramide) + psychosine = AR

Similar sounding: **Fabry** = **α-galactosidase A** deficiency

Krabbe = **galactocerebrosidase** deficiency

Krabbe and **galactocerebrosidase** both have a **b**

USMLE vignettes mention developmental delay and peripheral neuropathy in an infant with **optic atrophy**. The question might also mention that the infant was found to have **globoid cells with linear inclusions inside macrophages**. The term "**globoid cell**" is synonymous with Krabbe disease on Step1.

USMLE question writers like to see that you can differentiate Hurler vs Hunter syndromes.

As said before, Hunter syndrome and Fabry disease are both XR. That means if you're ever confronted with the genetics of Hurler vs Hunter syndrome:

"Hunters can shoot the target (X) with their arrows." Therefore Hunter must be the one that's XR, and Hurler AR.

Hurler syndrome = ↓ α-L-iduronidase = ↑ heparan sulfate + dermatan sulfate = AR

Hurler syndrome presents with **clouded corneas**, **gargoyle-like facies**, stridor (due to airway obstruction), frequent ear infections, valvular lesions and hepatosplenomegaly.

Hunter syndrome = ↓ iduronate sulfatase = ↑ heparan sulfate + dermatan sulfate = **XR**

Hunter syndrome presents generally as a milder version of Hurler and **without** clouded corneas. Remember, not only can hunters see their target (XR), but because they can literally see it, they **don't** have clouded corneas.

Does the infant have clouded corneas? Yes, has clouded corneas → Hurler syndrome (AR)

Does the infant have clouded corneas? No, does not have clouded corneas. → Hunter syndrome (XR)

I-cell disease = ↓ mannose-6-phosphate production = AR

Don't worry about the enzyme deficiency for I-cell disease. They just want you to know it's a syndrome that presents in a child as **coarse facial features** and stiff joints, where there's decreased ability to phosphorylate the 6th position on mannose.

This phosphorylation leads to failure to target hydrolases to the lysosomes. Therefore in this disease, if the vignette is obviously I-cell disease, the answer might be: **increased lysosomal hydrolases in the plasma**.

An important factoid for I-cell disease is that whilst it's technically a lysosomal storage disease, the failure of M6P production occurs in the **Golgi apparatus**. If they ask you the organelle associated with I-cell disease, **the answer is Golgi, not lysosomes!**

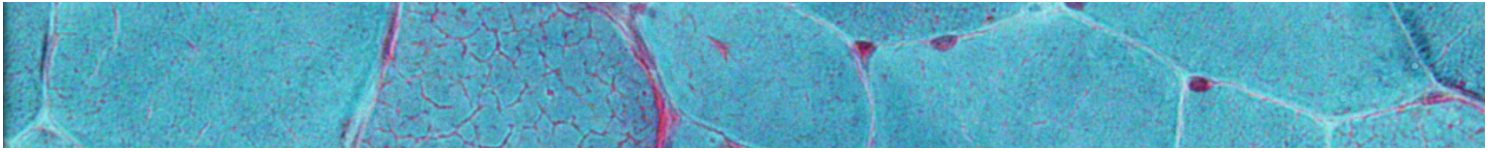
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1. Avascular necrosis of the femoral head in a child with a lysosomal storage disease. What's the diagnosis?

- ☐ Hurler
- ☐ Tay-Sach
- ☐ Hunter
- ☐ Gaucher
- ☐ Niemann-Pick
- ☐ Metachromatic leukodystrophy
- ☐ Fabry
- ☐ Krabbe

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BIOCHEMISTRY

Maple syrup urine disease

by MEHLMANMEDICAL

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In this condition, the USMLE will mention that there are increased levels of the α -ketoacids of **leucine, isoleucine and valine** in the blood because of deficiency of **α -ketoacid dehydrogenase**, a thiamine (vitamin B1)-dependent enzyme.

Leucine, isoleucine and valine are all **branched-chain amino acids**.

The vignette might mention that a mother notices the smell of “burnt sugar” in her infant’s diaper, and then the question will ask you which amino acid has defective metabolism. They’ll literally list all of the amino acids, and you’ll have to know that the disease was MSUD and that the answer is leucine, isoleucine or valine.

α -ketoacid dehydrogenase is a vitamin B1- dependent enzyme. So are transketolase, α -ketoglutarate dehydrogenase and pyruvate dehydrogenase.

If they ask you for the treatment, the answer is to restrict intake of leucine, isoleucine and valine.

MSUD is most prevalent in the Ashkenazi Jewish population.

Since **α -ketoacid dehydrogenase** is a thiamine-dependent enzyme, **if they ask you what could theoretically help mitigate metabolic derangement in the patient, the answer is thiamine**.

Symptoms include hypotonia, mental impairment, metabolic acidosis and hypoglycemia.

When broken down:

Leucine $\rightarrow$ acetyl-CoA $\rightarrow$ ketogenesis (since we’re in catabolic state)

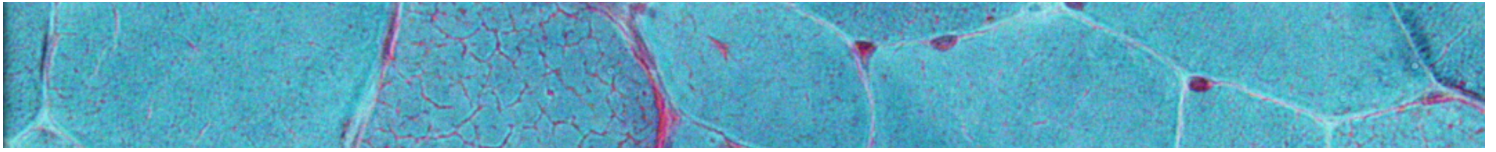
Isoleucine + valine $\rightarrow$ propionyl-CoA $\rightarrow$ succinyl-CoA $\rightarrow$ gluconeogenesis

That’s why leucine is strictly a ketogenic amino acid. It doesn’t enter the TCA cycle the same way that isoleucine and valine do.

That’s it. Nothing crazy dramatic.

—

1. What are the four thiamine-dependent enzymes?



BIOCHEMISTRY

Marfan syndrome

by MEHLMANMEDICAL

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Marfan syndrome genetics

- Autosomal dominant; chromosome 15; *FBN1* / *FBN2* genes
- *FBN1* / *FBN2* code for **fibrillin**, which is a glycoprotein that forms a sheath around elastin
- Marfan syndrome is **NOT** a collagen disorder.

Elastin and fibrillin work together. **Fibrillin is a glycoprotein that forms a sheath around elastin.** In other words, it forms a scaffold in which elastin can be deposited.

Once again, Marfan syndrome is not a collagen disorder.

The USMLE really wants you to be able to contrast elastin from collagen. (My HY post on collagen synthesis [is here.](#))

In contrast to collagen, elastin has:

- ↑ hydrophobic amino acids (alanine, valine, glycine)
- ↓ hydroxylation (only non-hydroxylated proline + lysine)
- No glycosylation, triple α -helix, or -S-S-heavy terminal regions.
- **Extensive desmosine crosslinking**
 - **Tropoelastin** is secreted into the extracellular matrix, where its lysine side-chains covalently interact to form **desmosine crosslinks**.
 - Extensive desmosine crosslinking is what enables elastin's resilient bending/stretching properties.
 - The desmosine crosslinking is catalyzed by lysyl oxidase.
- Once elastin is formed following desmosine crosslinking, it interacts with fibrillin.
- Fibrillin is a glycoprotein that forms a sheath around elastin. It forms a scaffold in which elastin can be deposited. (Correct, I'm telling you that for the third time)

HY Marfan syndrome features

- Tall and lanky, with arachnodactyly (long fingers); **arm-span greater than height** (>1.05x)
- Chest wall abnormalities (i.e., pectus excavatum/carinatum) → ↑ **risk for spontaneous pneumothorax**
- **Scoliosis**
- Pes planus (flat feet)

- Hyperextensible joints
- **Dural ectasia** (**lower back pain** caused by ballooning of the dural sac around the spinal cord)
- Lens dislocations (fibrillin is abundant in the zonules of Zinn [fibrous ring that stabilizes the lens])
- **Mitral valve prolapse, aortic regurgitation, aortic dissection**

If you get a stethoscope question in someone with Marfan syndrome, before you freak out about thinking you're not great at auscultating heart sounds, remember that you're looking for either AR or MVP.

AR = Decrescendo holodiastolic (pan-diastolic) murmur at the 2nd intercostal space, right sternal border

MVP = Mid-systolic click at the 4th intercostal space, left mid-clavicular line

- Patients with Marfan syndrome are **very tall** because bone elongation occurs 2° to unstable periosteum resulting in pathologic longitudinal growth.
- **Lens dislocations** are due to defective microfibrils within the suspensory ligaments.
- **Aortic regurgitation** and **aortic dissections** occur due to **weakening of the tunica media** (**cystic medial necrosis**).
- The **mitral valve prolapse** pathophysiology is described as **myxomatous degeneration** of the mitral valve. This term refers to **thickening and redundancy** of the mitral valve leaflets.

Hyperextensible skin and Circle of Willis berry (saccular) aneurysms are seen in **Ehlers-Danlos syndrome**, not Marfan syndrome.

These two distinctions are really HY on the USMLE!

What the fuck does "Marfanoid" mean?

- "Oid" means looks like but ain't.
- Fibrinoid means looks like fibrin, but it ain't fibrin. (Seen in polyarteritis nodosa)
- Plasmacytoid means looks like a plasma cell, but it ain't a plasma cell. (Plasmacytoid cells are seen in Waldenstrom macroglobulinemia)
- Marfanoid body habitus means the patient looks like he or she has Marfan syndrome but doesn't.

Homocystinuria = school-age child with Marfanoid body habitus, Hx of thrombotic event, and often blurry vision or lens dislocation

MEN 2B = Marfanoid body habitus, pheochromocytoma, medullary thyroid carcinoma, mucosal neuromas

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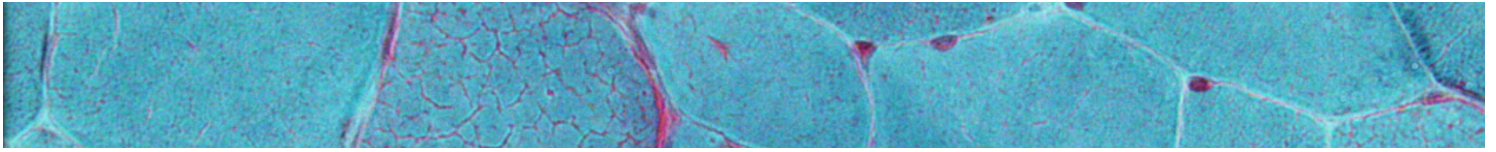
1. a) What is the inheritance pattern of Marfan syndrome?

b) Which chromosome number?

c) Which genes?

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BIOCHEMISTRY

Menkes syndrome

by MEHLMANMEDICAL

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This is an interesting disease that doesn't come up conversationally or in medical school lectures too often, but it is in fact tested on USMLE Step1. This is because its pathophysiology relates to [collagen synthesis](#), which is exceedingly HY on Step1.

Inheritance pattern and mechanism of disease

- Menkes syndrome (XR) and Wilson disease (AR) are essentially the opposite, where the latter is too much copper and the former too little.
- Menkes is characterized by a **decreased ability to absorb copper in the gut** due to a defective transporter (ATP7A).
- Wilson is due to an inability to secrete copper into bile (copper is normally excreted through bile).

Why we need copper

- It is a cofactor for **lysyl oxidase**, which is the final enzyme necessary in collagen synthesis.
- This means there is lesser activity of lysyl oxidase in Menkes syndrome secondary to copper deficiency.

On the USMLE, Menkes syndrome will present **very similarly** to [vitamin C deficiency \(scurvy\)](#). So be on the lookout and have Menkes syndrome as a DDx.

Menkes syndrome is characterized by connective tissue weakness, **brittle, "kinky" hair**, neurological disorders (including truncal hypotonia and seizures) and mental impairment.

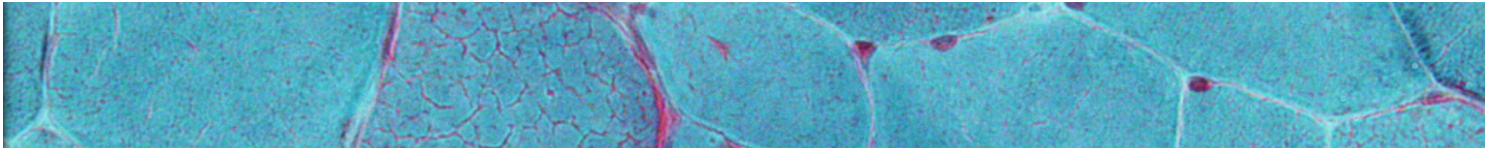
By far the most important thing to remember about Menkes disease is the **"kinky" hair**.

That's it.

—

1. What does the body use copper for?

- ☐ Cofactor for lysyl hydroxylase, the last enzymatic step in collagen synthesis
- ☐ Cofactor for lysyl hydroxylase, the penultimate enzymatic step in collagen synthesis
- ☐ Cofactor for lysyl oxidase, the last enzymatic step in collagen synthesis
- ☐ Cofactor for lysyl oxidase, the penultimate enzymatic step in collagen synthesis



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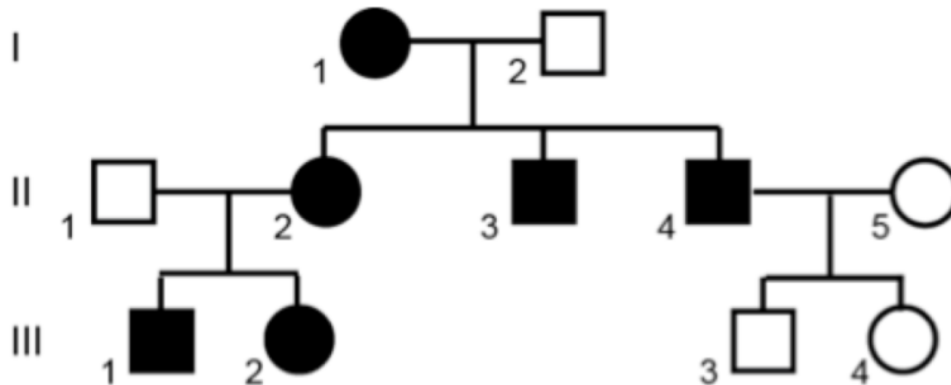
Mitochondrial disorders

by MEHLMANMEDICAL

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The mitochondrial genome demonstrates strict maternal inheritance.

- Highest yield point on the USMLE about mitochondrial disorders.
- Disease is inherited strictly through mothers.
- **Zero percent of fathers** pass mitochondrial diseases to offspring.

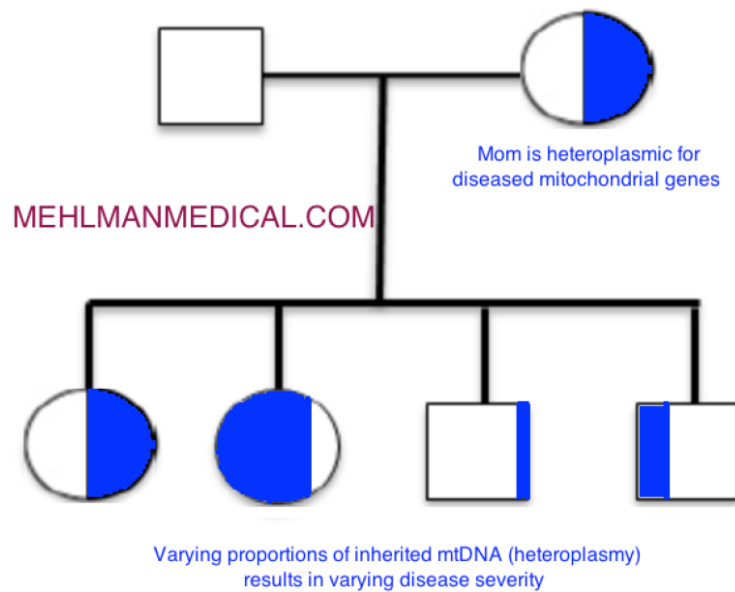
Mitochondrial disorders share very characteristic pathologies that are easy to identify in Qs

- The combination of **visual + hearing problems, hypotonia, and lactic acidosis** is exceedingly HY and reflective of a mitochondrial disorder.

Lactic acidosis is common in mitochondrial diseases; tissues with high metabolic rates are affected first (i.e., **muscle, eyes, ears, neural tissue**).

Heteroplasmy is exceedingly HY for mitochondrial genetics

- **Heteroplasmy** is the presence of more than one type of mitochondrial DNA in the same individual.
- This means there is a non-uniformity of mitochondrial genes inherited (i.e., some cells contain one type of mitochondrial genome; other cells contain a different type, similar to mosaicism).
- **In turn, mitochondrial diseases frequently vary in severity among individuals because of varying ratios of diseased vs wild-type mitochondrial genes inherited.**



Similar genetics terms:

Variable expressivity

- Everyone with diseased genotype has diseased phenotype (i.e., everyone with diseased gene shows it outwardly), but individuals merely vary in presentation.
- USMLE-favorite example is NF1, where some individuals may have, e.g., neurofibromas, cafe au lait spots, and pheochromocytoma, Lisch nodules, etc., whereas another individual might simply have axillary/groin freckling and that's it. **This even when both individuals may carry the same exact mutation.**
- In the case of heteroplasmy, the variable presentation among individuals is due to *different proportions* of diseased mitochondrial genes inherited.

Incomplete penetrance

- Not everyone with diseased genotype has diseased phenotype (i.e., not everyone shows it outwardly; it “skips” some people).
- An example is BRCA1/2 mutations – i.e., not everyone with the mutation will go on to develop cancer (usually breast).

“Ragged red fibers” is buzz-wordy for mitochondrial inheritance

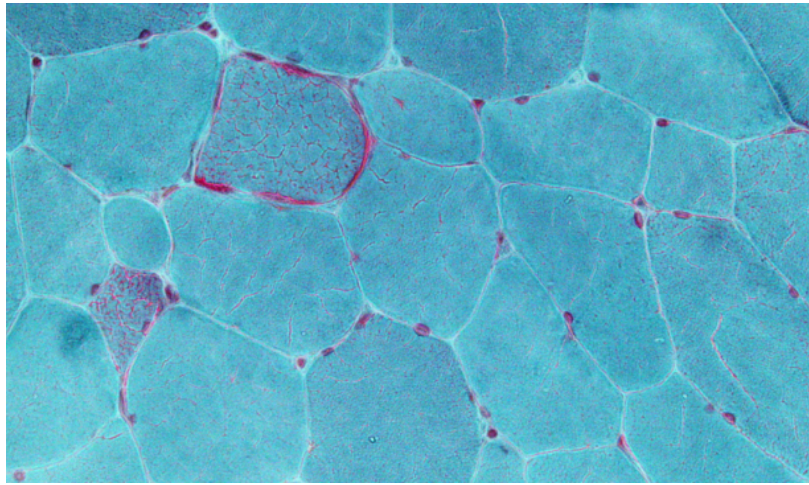
- Seeing “ragged red fibers” in a question for a mitochondrial inheritance is akin to seeing malar rash in an SLE question. Both too easy.

“Ragged red fibers” on microscopy is a phrase the USMLE likes to throw around for mitochondrial inheritance.

They're classically associated with MERRF syndrome (myoclonic epilepsy with ragged red fibers).

Myoclonic epilepsy with ragged red fibers (MERRF)

- This is a mitochondrial disorder characterized by **seizures**, ataxia, hearing loss, and myopathy.
- Ragged red fibers are abnormal mitochondria accumulating under the sarcolemma. They are red with trichrome stain.



If you look closely, you might be able to see ragged red fibers. Don't worry, you'll never need to rely on an image like this on the real exam. They'll just tell you in the vignette literally, "ragged red fibers." (Image compliments of Wiki)

MELAS

- MELAS stands for **mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes**.

Leber hereditary optic neuropathy

- Characterized by painless, subacute, usually adult-onset (classically males in their 20s) **bilateral blindness** w/ multiple sclerosis-like Sx, movement disorders, and arrhythmia.

Kearns-Sayre syndrome

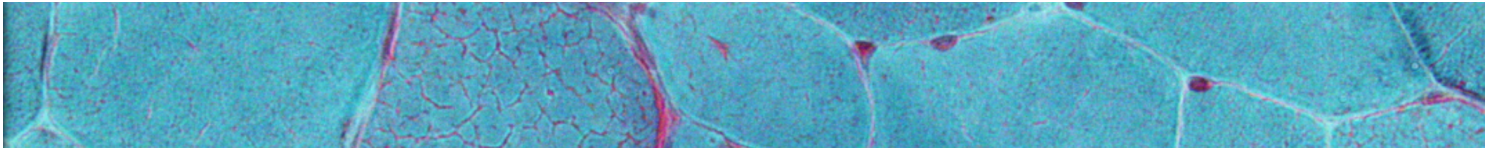
- Characterized by progressive ophthalmoplegia, pigmentary retinopathy, cerebellar ataxia, and heart block.

—

1. In what pattern are mitochondrial diseases inherited?

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BIOCHEMISTRY

Phenylketonuria (PKU)

by MEHLMANMEDICAL

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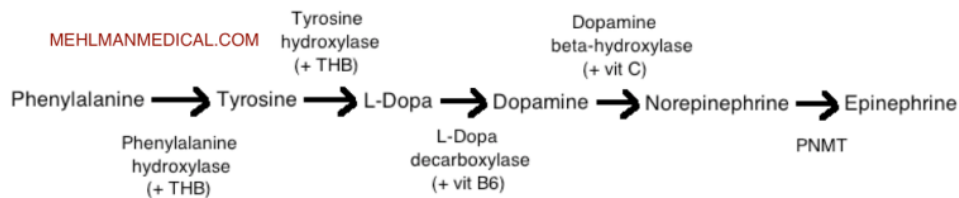
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Almost always, PKU is due to **deficiency of phenylalanine hydroxylase**.

Rarely, it can also be due to deficiency of tetrahydrobiopterin (THB). This type is called malignant PKU.

Deficiency of phenylalanine hydroxylase = classic phenylketonuria

Deficiency of tetrahydrobiopterin = malignant phenylketonuria



Notice that THB is a cofactor for both phenylalanine hydroxylase and tyrosine hydroxylase. In PKU, whether classic or malignant, **the treatment is ↓ phenylalanine and ↑ tyrosine in diet**.

The difference is that in malignant PKU, once tyrosine is given as Tx, it cannot be converted efficiently to L-Dopa (and further to dopamine).

Therefore:

In malignant PKU, **galactorrhea (hyperprolactinemia)** can result from ↓ dopamine secondary to ↓ L-Dopa. In classic PKU, there is no hyperprolactinemia because tyrosine can still be converted to L-Dopa.

In both forms of PKU, there is mental impairment if phenylalanine is not removed from the diet. **Aspartame**, an artificial sweetener found in many diet beverages, contains phenylalanine and must be avoided in PKU patients.

Eczema, fair skin and “musty” or “mousy” body odor are common USMLE findings.

One other important point about PKU is its relation to pregnancy. Let's say the fetus does not have PKU, but the mom does. If the mom does not strictly watch her diet while pregnant, small elevations in blood phenylalanine **can cause mental impairment and signs of PKU in the fetus**. This is because lack of maternal enzyme can lead to increased phenylalanine crossing the placenta to the fetus. **This is called maternal PKU.**

In contrast, let's say the fetus *actually does* have PKU but the mom is a mere carrier (i.e., does not have PKU). A normal maternal diet (i.e., no restriction of phenylalanine) will not lead to symptoms of PKU in the fetus because the mother still has sufficient enzyme to metabolize the phenylalanine.

PKU is screened for in newborns via a heel-prick test because it is a preventable cause of mental retardation. This PKU screening test (and screening tests in general) must be very **sensitive** because a false (-) result could have devastating consequences.

1. Which of the following is the correct order for catecholamine synthesis?

- ☐ Tyrosine → Phenylalanine → L-dopa → Dopamine → Norepinephrine → Epinephrine
- ☐ Tyrosine → Phenylalanine → L-dopa → Dopamine → Epinephrine → Norepinephrine
- ☐ Phenylalanine → Tyrosine → L-dopa → Dopamine → Norepinephrine → Epinephrine
- ☐ Phenylalanine → Tyrosine → L-dopa → Dopamine → Epinephrine → Norepinephrine

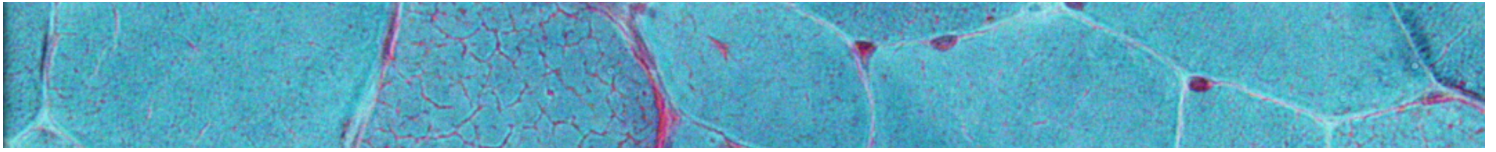
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HY USMLE Q #940 – Biochemistry

January 1, 2024



BIOCHEMISTRY

Phakomatoses

by MEHLMANMEDICAL

Phakomatoses is that obscure term that pretty much causes every convo with a student to go like this:

“Wait, what... what did you just say?”

“Phakomatoses.”

“Phakomatoses?? What the fuck is that.”

Phakomatoses are neurocutaneous disorders and refer to:

- **NF1, NF2, TSC, VHL, and Sturge-Weber.**

Neurofibromatosis type I (NF1)

- Chromosome 17
- Autosomal dominant
- Neurofibromas (benign cutaneous nerve tumors presenting as small, soft bumps on the skin)
- Axillary and groin freckling
- Lisch nodules (iris hamartomas)
- **Cafe au lait spots** (hyperpigmented macules)
- **Pheochromocytoma**
- **Optic nerve glioma**
- Glioblastoma multiforme
- Demonstrates variable expressivity

Neurofibromatosis type II (NF2)

- Chromosome 22
- Autosomal dominant
- **Bilateral acoustic schwannomas**
- Congenital cataracts
- Meningioma, ependymoma, oligodendroglioma, medulloblastoma

Tuberous sclerosis (TSC)

- TSC1 gene on chromosome 9 coding for hamartin protein, and chromosome 16 coding for tuberlin protein.
- Autosomal dominant
- Periventricular nodules seen on CT or MRI (tubers)
- Presents as seizure in young child (Qs like writhing movements in a kid's sleep)
- Adenoma sebaceum (angiofibromas; skin-colored papules in a butterfly distribution on the face and in the nasolabial folds)
- Subungual fibromas (nailbed tumors)

- Cardiac rhabdomyoma
- Renal angiomyolipoma
- Pulmonary lymphangioleiomyomatosis (abnormal smooth muscle proliferation of airways; can also affect pregnant women who do not have TSC)

von Hippel-Lindau (VHL)

- Chromosome 3
- Autosomal dominant
- Cerebellar and retinal hemangioblastomas
- Bilateral renal cell carcinoma
- Constitutive activation of hypoxia-inducible factor (HIF), leading to vascular proliferation

Sturge-Weber syndrome

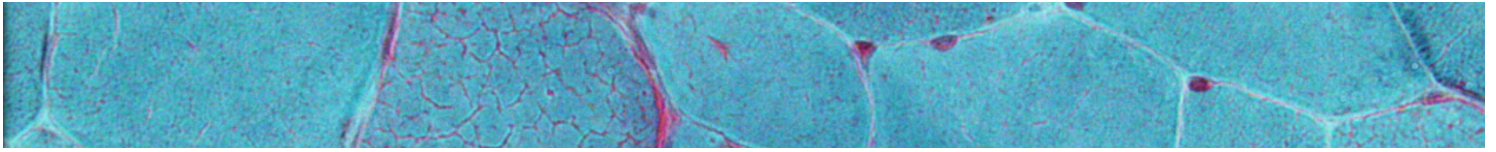
- Not hereditary; caused by mosaic, somatic mutation in GNAQ gene
- Unilateral facial Port-wine stain birthmark (**but may also present as cutaneous violaceous papules in an ophthalmic-trigeminal nerve distribution**)
- Seizure
- Ipsilateral leptomeningeal angioma (arachnoid or pia mater vascular tumor)
- Glaucoma

—

1. What's the inheritance pattern of the phakomatoses?

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BIOCHEMISTRY

Regulation of glycogen metabolism

by MEHLMANMEDICAL

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An important point about glycogen metabolism is the functionality of glycogen phosphorylase. This enzyme is most upstream and breaks down glycogen from its most branched form.

Now what I'm about to write is going to sound really ridiculous and pedantic:

During the fasting state, glycogen phosphorylase and glycogen phosphorylase kinase are **activated and phosphorylated**.

Mike, the USMLE seriously cares about enzyme phosphorylation? **Yeah.**

Glycogen phosphorylase kinase is simply the enzyme that phosphorylates and activates glycogen phosphorylase.

Both are phosphorylated AND activated during the **fasting** state.

^ Yes, just memorize that. I promise I'm not wasting your time.

The way to approach this topic is to know that **insulin generally causes dephosphorylation of enzymes**.

So for starters:

Fed state? → insulin high → enzymes dephosphorylated

Fasting state? → insulin low → enzymes phosphorylated

Then we have:

Fed state? → we expect anabolic enzymes active + catabolic enzymes inactive

Fasting state? → we expect catabolic enzymes active + anabolic enzymes inactive

So now let's combine the two:

Fed state? → insulin high + anabolic enzymes active + catabolic enzymes inactive

Fasting state? → insulin low + catabolic enzymes active + anabolic enzymes inactive

Now finally, introducing the phosphorylation aspect:

Fed state? → insulin high → anabolic enzymes dephosphorylated + active; catabolic enzymes dephosphorylated + inactive

Fasting state? → insulin low → catabolic enzymes phosphorylated + active; anabolic enzymes phosphorylated + inactive

So for instance, PFK2 is an anabolic enzyme, so if they tell you a guy just ate a turkey dinner, you'd say:

"Ok, well insulin would be high. Therefore, whatever enzyme they're asking about would be dephosphorylated. Because PFK2 is anabolic, it's clearly going to be active in the fed state, so we can say it's dephosphorylated and active."

Sound really dry and boring? Yeah, I know. But the USMLE doesn't give a fuck about how dry you think this is. The rule is that whatever you choose not to study is going to be exactly what shows up on your test.

The reason the phosphorylative processes occur as they do is because insulin is always in a balance with glucagon. The latter up-regulates cAMP synthesis, which activates protein kinase A (PKA), which in turn phosphorylates enzymes. Insulin, however, despite acting through a MAP kinase, ultimately leads to activation of protein phosphatases that dephosphorylate enzymes.

Really annoying detail that seemingly contradicts the above:

If you are ever asked in a question about insulin's effect on intracellular signaling, it phosphorylates via MAP in order to ultimately increase gene transcription. But when we're talking about the macro effect of enzyme activation / inactivation, insulin **dephosphorylates**. This is asked on one of the NBMEs (i.e., when insulin binds to its receptor, what happens in its signaling pathway → yes, phosphorylation; yes, gene transcription; no, no proteolysis).

Two other points:

Although glucagon secretion during exercise (fasting state) contributes to maintenance of blood glucose levels, **if they ask you what ensures that muscle contraction/activity is coordinated with glycogen breakdown, the answer is calcium.**

You need to know that calcium/calmodulin leads to the phosphorylation and activation of glycogen phosphorylase kinase. Although calmodulin is responsible for contraction only in smooth muscle, in skeletal muscle, it still has a major role in regulation of glycogen catabolism.

And the other key detail: **glucocorticoid (i.e., cortisol) INCREASES glycogen synthesis, despite being catabolic in muscle/adipose tissue.**

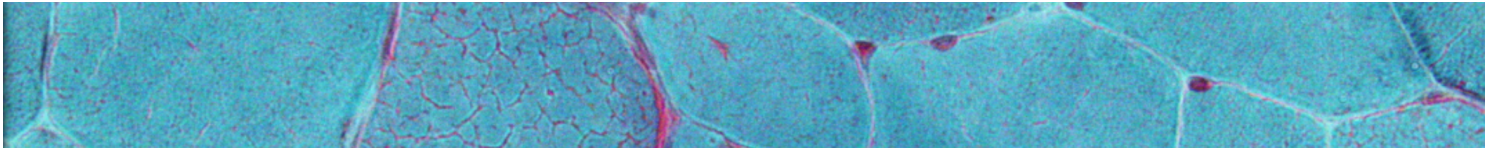
You would think that because cortisol is catabolic it would increase glycogenolysis, **but it instead increases glycogenesis** (at least in USMLE questions).

That's pretty much it on this annoying topic.

—

1. Guy runs 10 miles. Which of the following best describes his glycogen phosphorylase?

- ☐ Phosphorylated; inactive
- ☐ Phosphorylated; active
- ☐ Dephosphorylated; inactive
- ☐ Dephosphorylated; active



BIOCHEMISTRY

Trinucleotide repeat (TNR) disorders

by MEHLMANMEDICAL

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Four you need to know for the USMLE:

1. Fragile X (CGG; FraGile X)
2. Huntington disease (CAG; AGreat Hunter)
3. Friedreich ataxia (GAA; AtaxiA)
4. Myotonic dystrophy (CTG; MyoTonic)

TNR diseases demonstrate **anticipation**, which is an $\uparrow$ in the # of codon repeats with each successive generation.

The # of repeats directly correlates with the severity of the condition and inversely correlates with age of onset.

$\uparrow$ repeats = $\uparrow$ severity of condition + $\downarrow$ age of onset

USMLE will tell you, e.g., a guy with Huntington develops features at age 32, and that his dad had similar findings starting in his 40s. Answer = anticipation. Not super complicated.

Huntington disease

Caused by CAG repeat expansion

- Huntington disease is an **AD** disorder of the **huntingtin gene** on **chromosome 4** (although the disease is spelled Huntington, the gene is huntingtin).
- Knowing specifically that it is **AD** and on **chromosome 4** is one of the highest yield points for genetics on the Step 1.
- Disease presents when the **CAG (AGreat Hunter)** repeats are >40 . 36-39 is considered premutation, with anticipation almost certainly leading to disease in the next generation.

Choreoathetosis and cognitive decline are the hallmark clinical features

- Chorea = fast, jerky movements.
- Athetosis = slow, writhing movements.
- Progressive dementia/cognitive decline generally ensues from the 30s or 40s onward, depending on # of CAG repeats.

USMLE wants you to know where in the brain is affected

- Choose **caudate nuclei** and **putamen** as the areas of the brain that are affected.
- There is also **dilatation/widening of the anterior horns of the lateral ventricles**.

Most common cause of death is (weirdly) pneumonia

- The leading cause of death is **pneumonia** secondary to aspiration from ↓ muscle coordination.

USMLE loves turning Huntington disease into an ethics scenario

If a patient requests genetic testing because he or she has a parent with known Huntington disease, you **DO NOT** do testing right away.

Genetic counseling is mandatory beforehand.

Huntington disease demonstrates **complete penetrance**. If the patient has 40 or more repeats, there is 100% chance he or she will develop the disease.

Neurotransmitter irregularities are HY

- The USMLE might also tell you a patient with progressive dementia died and brain biopsy reveals protein strands with long **glutamine** repeats.
- The CAG codon codes for **glutamine**, so you need to remember **CAG = glutamine**.
- Hormonally, the disease is characterized by **increased dopamine** and **decreased GABA** and **acetylcholine**.
- The **decreased GABA** is very high-yield.

For Huntington, choose ↓ GABA | ↓ ACh | ↑ Dopamine

Treatment for Huntington

- The disease is **incurable** but can be palliated with amine-depleting drugs, such as **tetrabenazine** and **reserpine**.
- Both of these drugs **inhibit VMAT** (vesicular monoamine transporter).
- VMAT is necessary for the packaging of catecholamines into vesicles and their subsequent release into the synaptic cleft.
- If VMAT is inhibited, free, unprotected dopamine within the presynaptic cleft is degraded by monoamine oxidase.
- **Typical antipsychotics** (e.g., haloperidol) are also used in the treatment of Huntington-associated psychosis.

Fragile X syndrome

Caused by CGG repeat expansion

- The disease gets its name because of X-chromosome fragility when CGG (FraGile) repeats exceed 200.
- The increased number of repeats causes gene methylation, which is identified when karyotyping is performed on leukocytes in a **folate- and thymidine-deficient** medium.
- Disease is **X-linked recessive**, not dominant. If a female has mild clinical features, it's due to skewed lyonization (X-inactivation).

Physical presentation is very HY for the Step

- Most salient characteristics in any USMLE question are **large, everted ears**, **long jaw**, and **macroorchidism** (large testes).
- Be on the lookout for a boy (X-linked) with a long, narrow head and big ears who has intellectual impairment.
- There is also joint laxity, **scoliosis**, and **pes planus** (flat-footedness).

USMLE is tricky when contrasting fetal alcohol syndrome (FAS) with Fragile X

- Fetal alcohol syndrome is the most common cause of mental retardation overall. Most important characteristic in any vignette is a **long, smooth, flat philtrum**.
- If the USMLE gives you a boy with ↓ IQ who has large, everted ears and **any change to his philtrum**, the answer is **FAS**, not **Fragile X**.

The USMLE is known to be very difficult with FAS questions. The vignette might sound entirely like Fragile X, but if they mention somewhat incidentally that the philtrum is flat, long, or smooth, choose FAS, not Fragile X.

Myotonic dystrophy

Caused by CTG repeat expansion

- Myotonic dystrophy is an AD disease on chromosome 19, with an expansion of CTG (MyoTonic dystrophy).
- This leads to abnormal expression of a **myotonin-protein kinase**, a type of serine-threonine kinase.

Presentation is generally easy on the USMLE

- Characterized by **sustained muscle contraction**, muscle wasting, baldness, cataracts, and testicular atrophy.
- The key feature is the sustained muscle contraction, where the individual **will demonstrate an inability to relax his or her muscles**.
- This shows up in questions as an **extra-long handshake** or **not being able to let go of the golf club or doorknob**.

Friedreich ataxia

Caused by GAA repeat expansion

- Friedreich ataxia is an AR disorder on chromosome 9, with an expansion of **GAA** (Friedreich Ataxi**A**).
- USMLE wants you to know the gene is called **frataxin**. Do **NOT** confuse this with Fragile X, which is the **FMR1** gene.

HY findings

- May present with **cardiomyopathy**. Sources differ as to whether hypertrophic or dilated is more common. But the USMLE will give you a clear presentation as to which one they're referring to.
- If hypertrophic, the patient will have a severely thickened LV and (often) an S4 heart sound; there will be diastolic dysfunction (↑ diastolic filling pressure + preserved ejection fraction). If dilated, there will be a lateralized apex beat / apical impulse, a dilated cardiac silhouette, and an S3 heart sound.
- **Early-onset T2DM** is a notable feature.
- **Kyphoscoliosis** and **pes cavus** (high-arched foot) are HY.
- The disorder is characterized by (obviously) **ataxia**, Babinski reflexes, dysarthria, and **hammer toes** (contraction deformity of toes).

—

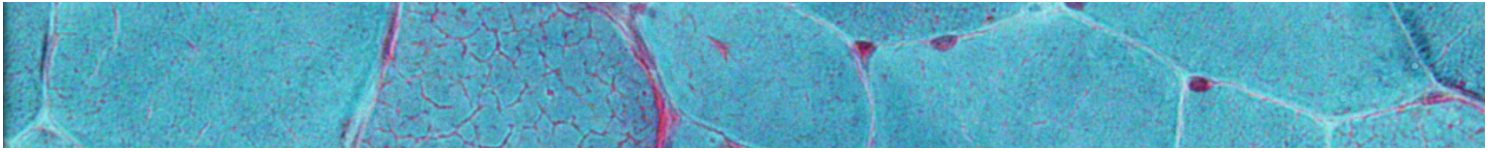
1. What are the four trinucleotide repeat (TNR) disorders, and what are their repeats?

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BIOCHEMISTRY

Urea cycle, Orotic aciduria, OTC deficiency

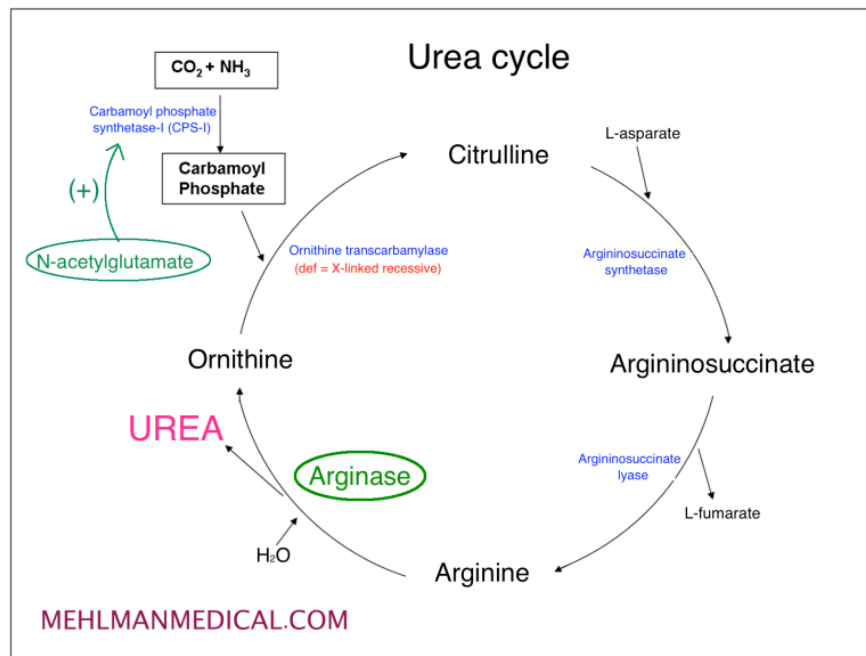
by MEHLMANMEDICAL

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Let's face it, the urea cycle is dry and annoying as fuck, but you don't have to memorize it like this is undergraduate biochemistry.



The rate-limiting enzyme is CPS-I. I circle **arginase** and **N-acetylglutamate** for an important reason.

I was in Pittsburgh for New Years 2011-2012, just before I started studying for my own Step 1. I was at a pizza place, and there were two guys in line with me talking about medicine. As it turns out, they were residents in radiology and surgery and had aced their Steps. Call it dumb and dorky all you want, but I started asking them about how to prepare for the Step.

Correct, of all times to talk about USMLE, I did it on New Years.

One of the guys, super-drunk and with eyes wide-open, said to me:

"Arginase.....Know arginase.....It's the last enzyme in the urea cycle. It's the actual one that makes urea."

I was like, “Okay, got it. I’ll make sure to remember that.”

And he goes, “No...you don’t understand...that was on my exam. They asked ARGINASE. You need to know ARGINASE.”

I remember leaving the pizza place thinking it was like the movie The Matrix, as though I had met the Oracle who intervened and told me what was going to be on my exam. I remembered that detail the whole next year, convinced it would show up on my Step. It never did. But I’ve always made sure to tell my students that detail either way.

I’ll say, “Look, it’s dumb I know. The urea cycle is dry and boring as fuck. But just know arginase. It’s apparently asked.”

And one of my students once got back to me after the exam and said it showed up. They were like wow wtf thank you.

So as I said, know arginase. Hopefully that mini-story makes it stick.

—

The USMLE also has some sort of magical obsession with **N-acetylglutamate**.

Yes, for some undisclosed magical reason, the USMLE is infatuated with **N-acetylglutamate**. Just know it’s a positive allosteric regulator of CPS-I. I promise you this shows up.

In questions, they’ll tell you that a patient has **hyperammonemia**, there is increased ornithine, and that urea cycle enzyme levels are normal. The answer is N-acetylglutamate deficiency.

—

The USMLE also really wants you to know that **ornithine transcarbamylase (OTC) deficiency is X-linked recessive**. I do not know why, but that is high-yield in urea cycle questions.

They also want you to be able to contrast between OTC and orotic aciduria.

Orotic aciduria is a condition of impaired pyrimidine biosynthesis, where orotic acid is an important precursor molecule that cannot be converted to downstream intermediates. It is caused by deficiency of the enzymes OPRT and ODC (you won’t get asked these).

In both OTC deficiency and orotic aciduria, increased serum orotic acid is seen, however there are some key differences:

In OTC deficiency, because the urea cycle is impaired, blood urea nitrogen (BUN) is lower. There is, however, a buildup of ammonia because of the failure to convert it to urea (BUN). In addition, there is no impairment in pyrimidine synthesis, so MCV is normal.

In orotic aciduria, the urea cycle is intact, so serum ammonia and BUN are normal. However MCV is increased because pyrimidine synthesis is impaired.

Patient has ↑ serum orotic acid:

Normal MCV, hyperammonemia, ↓ BUN → OTC deficiency (X-linked)

↑ MCV, normal ammonia + BUN → Orotic aciduria (AR)

In orotic aciduria, there’s an actual impairment of pyrimidine synthesis, so there’s slowed bone marrow production of nucleated erythrocyte precursors.

But in OTC deficiency, there’s merely a shunting of carbamoyl phosphate toward the pyrimidine biosynthesis pathway (where orotic acid is produced), so the latter is incidentally increased, but there’s no impaired pyrimidine synthesis.

That’s it. Yes, we could sit here and talk about # of ATP used, etc., + what occurs in the cytosol vs mitochondria, but the point is to get you a high score on the USMLE, not to give you an unabridged, boring as fuck college biochemistry lecture.

1. What is N-acetylglutamate?

- ☐ (+) allosteric regulator of ornithine transcarbamylase, the rate limiting step of the urea cycle
- ☐ (+) allosteric regulator of ornithine transcarbamylase, although not the rate limiting step of the urea cycle
- ☐ (+) allosteric regulator of carbamoyl phosphate synthetase I, the rate limiting step of the urea cycle
- ☐ (+) allosteric regulator of carbamoyl phosphate synthetase I, although not the rate limiting step of the urea cycle
- ☐ (+) allosteric regulator of carbamoyl phosphate synthetase II, the rate limiting step of the urea cycle
- ☐ (+) allosteric regulator of carbamoyl phosphate synthetase II, although not the rate limiting step of the urea cycle

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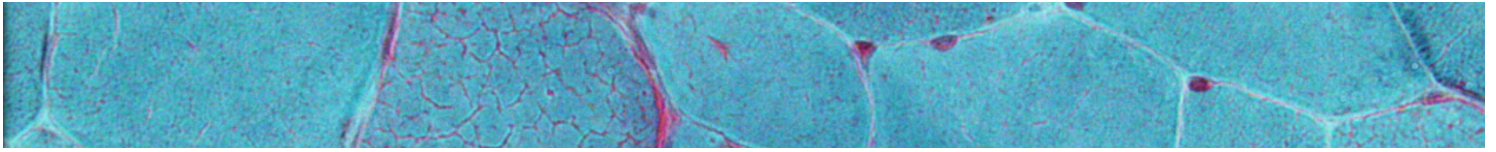


HY USMLE Q #940 – Biochemistry

January 1, 2024



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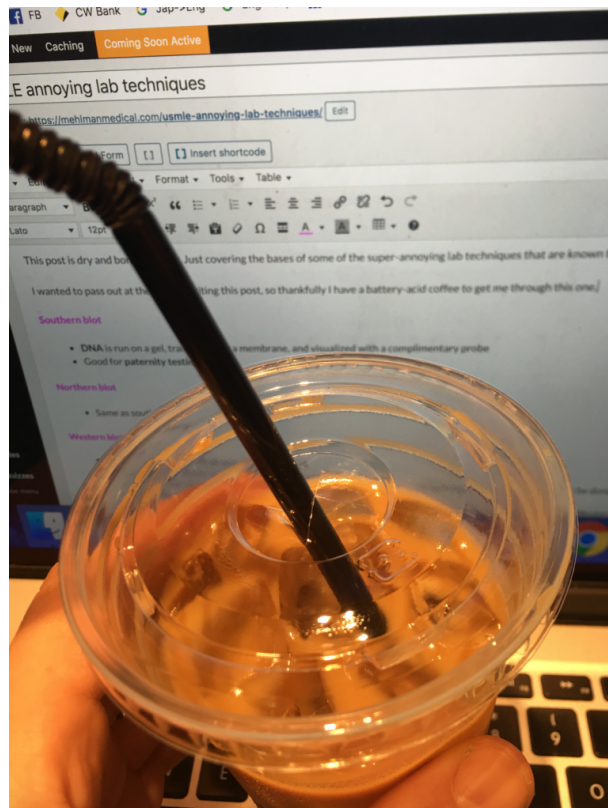
BIOCHEMISTRY

USMLE annoying lab techniques

by MEHLMANMEDICAL

Just covering the bases of some of the super-annoying lab techniques that are known to show up on the Step 1.

I wanted to pass out at the idea of writing this post, so thankfully I have a battery-acid coffee to get me through this one.



What, you didn't believe me? This is me writing the post as we speak.

Southern blot

- DNA is run on a gel, transferred to a membrane, and visualized with a complimentary probe
- Good for **paternity testing**

Northern blot

- Same as southern blot but with **RNA**, not DNA.

Western blot

- Same technique, but with **protein**, not nucleic acid.
- The protein is visualized using a complimentary antibody.
- This is the answer whenever they ask for the **confirmatory test** for HIV (p24 antigen testing, a newer test, can also be done, but Western blot is the gold standard confirmatory test)
- It is also the answer when they ask for how to **confirm Lyme disease** (serologies are also used, but the USMLE tests Western blot for Lyme).

Western blot is almost always the answer to “what is the confirmatory test?”

For HIV, ELISA is the sensitive screening test (↓ false-negatives); Western blot is the specific confirmatory test (↓ false-positives).

Either PCR or HIV culture is used in neonates.

Southwestern blot

- A type of Western blot
- A protein is run on a gel and then visualized with an oligonucleotide probe.
- This is great for **identifying DNA-binding proteins**.

Restriction fragment length polymorphism (RFLP)

- Restriction enzymes are used to digest DNA
- The DNA fragments are then separated according to length
- Although a relatively obsolete technique, on the Step1, it has been known to show up as another way to do **paternity testing**.

DNA fingerprinting

- A DNA technique that is used for **paternity testing** and **forensics**
- Looks at **variable number tandem repeats** (VNTRs), which are short DNA sequences that differ in number of repeats among individuals.

On the USMLE, Southern blotting, RFLP and DNA fingerprinting are all techniques used for paternity testing. Thrilling.

DNA microarray

- A chip hybridized with RNA and/or DNA probes is used to simultaneously detect expression of thousands of genes
- For the Step 1, the only thing you need to know about this technique is that it is able to detect **single nucleotide polymorphisms (SNPs)**.

Sequencing

- Uses dideoxynucleotides to randomly terminate growing strands of DNA, then the DNA is separated on a gel and read by the order of the bands on the gel.
- Just know this description refers to sequencing.

Polymerase chain reaction (PCR)

- Used to amplify a DNA fragment in order to make many copies
- The two DNA strands are **separated at high temperature**
- They are then amplified using a **heat-stable DNA polymerase** and **two different primers** (one for each strand) that **anneal** to the separated strands at **lower temperature**.

You might be given a dsDNA sequence asked to pick the primers.

If you are given, e.g.:

3' ATGACTAGCTAGA 5' = non-coding strand

5' TACTGATCGATCT 3' = coding strand

Bear in mind that DNA synthesis always occurs 5'→3' and you need a primer that can amplify each strand.

One of the primers will be **complimentary to the 3'-end of the coding strand**; the other primer will be identical to the 5'-end of the coding strand.

Therefore, the primers would be:

5' TACTGA 3' (identical to 5'-end of coding strand; amplifies the 3'-end of the non-coding strand in the 3'→5' direction and is synthesized 5'→3'), and

5' AGATCG 3' (complimentary to 3'-end of coding strand; amplifies the 3'-end of the coding strand in the 3'→5' direction and is synthesized 5'→3').

Reverse transcription PCR is used to detect mRNA levels. The mRNA is first converted to cDNA, then PCR is done.

When determining genotype (e.g., of an embryo, when both parents are CF carriers), isolate DNA, **run PCR first**, then do a Southern blot.

Enzyme-linked immunosorbent assay (ELISA)

- **Sensitive test** (↓ false-negatives) and is commonly used as a **screening test**
- As mentioned above, the USMLE is obsessed with you knowing that ELISA is the main screening test for HIV
- Two main types of ELISA tested on Step 1: direct and indirect
 - **Direct ELISA** = you are trying to detect antigen in the patient's serum
 - **Indirect ELISA** = you are trying to detect antibody in the patient's serum

Direct ELISA

- Coat a well with **known antibody**.
- Add patient's serum. If the **antigen** is present in the serum, it will bind the antibody on the well.
- So now there is a well with an Ab-Ag complex bound to the well.
- Now add **secondary antibody** (Ab₂).
- This secondary antibody (anti-human immunoglobulin) is bound to a **horseradish peroxidase enzyme** (Ab₂-E) that is capable of oxidizing a chromogen (substrate that produces color when oxidized).
- So now there's a well with Ab-Ag-Ab₂-E bound.
- Then the chromogen is added.
- The enzyme on the Ab₂ oxidizes it and color is generated.
- This color is measured using an absorbance reader.

So for direct ELISA, since you are trying to detect **antigen** in the patient's serum, you need the plate to initially be coated with **known antibody**.

This also means that the secondary antibody binds the patient's antigen.

Indirect ELISA

- Coat a well with **known antigen**.
- Add patient's serum. If the **antibody** is present in the serum, it will bind the antigen on the well.
- So now there is a well with an Ag-Ab complex bound to it.
- Then add **secondary antibody** (Ab₂). For indirect ELISA, this is called **anti-Human immunoglobulin**.
- This secondary antibody (anti-human immunoglobulin) is bound to a **horseradish peroxidase enzyme** (Ab₂-E) that is capable of oxidizing a chromogen (substrate that produces color when oxidized).
- So now there's a well with Ag-Ab-Ab₂-E bound.
- Then the chromogen is added.
- The enzyme on the Ab₂ oxidizes it and color is generated.
- This color is measured using an absorbance reader.

So for indirect ELISA, since you are trying to detect **antibody** in the patient's serum, you need the plate to initially be coated with **known antigen**.

This also means that the secondary antibody binds the patient's antibody.

- In indirect ELISA, the secondary antibody binds the Fc region of the primary antibody because the primary antibody's Fab regions are bound to the antigen coating the well.

For either direct or indirect ELISA, if they ask you for the name of the enzyme that is coupled to the Ab₂, the answer is horseradish peroxidase.

For indirect ELISA, if they ask you for the name of the secondary antibody that binds the patient's antibody, the answer is anti-human immunoglobulin.

An antibody monomer has one Fc region and two Fab fragments.

Papain cleaves antibodies into one Fc region and **two separate Fab fragments**. → (1 Fc + 2 Fab)

Pepsin cleaves Abs into one Fc region and two connected Fab fragments. → (1 Fc + 1 (Fab)₂)

Just remember that Pepsin chops the whole Ab in half; Papain doesn't.

—

1. Match correctly. (Select all that apply)

- ☐ RNA – Southern blot
- ☐ RNA – Northern blot
- ☐ RNA – Western blot
- ☐ DNA – Southern blot
- ☐ DNA – Northern blot
- ☐ DNA – Western blot
- ☐ Protein – Southern blot
- ☐ Protein – Northern blot
- ☐ Protein – Western blot

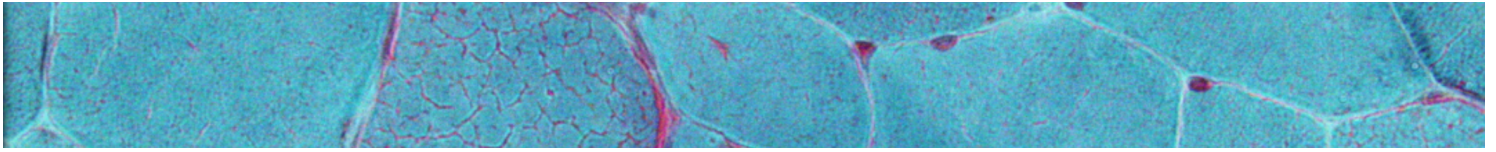
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BIOCHEMISTRY

Vitamin A, Zinc, Selenium

by MEHLMANMEDICAL

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Vitamin A in general

Vitamin A is a fat-soluble vitamin, as are D, E, and K. (All Dogs Eat Kittens).

Three main physiologic roles of vitamin A that you need to know for the Step1:

- 1) Is converted from 11-*cis*-retinal to 11-*trans*-retinal in phototransduction. Any vignette that mentions nyctalopia (night blindness) in relation to nutrition = vitamin A deficiency.
- 2) Supports proper immune functioning (i.e., deficiency → ↑infections)
- 3) Enables differentiation of tissues (i.e., prevents skin cancer via inhibiting squamous metaplasia).

Vitamin A as a treatment

The USMLE is also obsessed with the fact that all-*trans*-retinoic acid (a vitamin A derivative) can treat acute promyelocytic leukemia (AML subtype M3). This is because vitamin A induces differentiation of leukemic cells into mature neutrophils.

In the past, there have been studies demonstrating the effectiveness of vitamin A in treating measles. USMLE Step1 likes this. God knows why. Therefore, vitamin A deficiency = ↑susceptibility to measles. Know that.

The sequence of treatment for acne is generally as follows (yes, you need to know this; this is not pedantic; acne is one of the most common conditions in the population):

Topical retinoids (e.g., tretinoin gel) → topical benzoyl peroxide → topical clindamycin → oral tetracycline → oral isotretinoin

If you talk to a dermatologist, he or she will tell you there are different types of acne and regimens can sometimes differ. But the above sequence is for most patients. Particularly knowing topical retinoids are first, followed by benzoyl peroxide, is HY.

Isotretinoin, used to Tx severe acne, is oral high-dose vitamin A that is **teratogenic**. Before you administer this drug to a female of child-bearing age, perform a β-hCG.

If the USMLE asks you how vitamin A (retinoids) works for acne, the answer is:

1) It is a transcription factor.

2) It shuts off sebum production.

Both are bolded because of their high-yieldness.

Tangentially, benzoyl peroxide opens pores and kills bacteria.

Vitamin A deficiency

Vitamin A deficiency *and* excess have been known to cause **xerosis cutis**, aka **DRY SKIN**.

Bitot spots (grey plaques on conjunctiva) and **corneal metaplasia/necrosis** can be seen in severe vitamin A deficiency.

As mentioned above, vitamin A deficiency can increase risk of cancer, notably squamous cell carcinoma, as well as theoretically increase the risk of measles in a population.

Hypervitaminosis A (toxicity)

The two most common causes of vitamin A toxicity tested on Step1 are **isotretinoin** and **consumption of ursine (bear) liver**. Liver has the highest concentration of vitamin A compared to any other food.

The most commonly tested consequences of vitamin A toxicity are **increased intracranial pressure (pseudotumor cerebri)**.

Be on the lookout for papilledema and cerebral edema.

Hypervitaminosis A, obesity, danazol, and OCPs are notable Step1-tested causes of pseudotumor cerebri.

Whereas the other fat-soluble vitamins are stored in adipocytes systemically, vitamin A is notably concentrated in the liver in **hepatic stellate cells (aka Ito cells)**. These cells are found in the perisinusoidal space (space of Disse) and differentiate into myofibroblasts, which produce collagen, during hepatic fibrosis/cirrhosis.

Excess vitamin A is also teratogenic.

If they ever ask you what vitamin A teratogenicity results in: **Answer = cleft lip/palate**.

If they ever ask you about why vitamin A is a teratogen: **Answer = disrupts homeobox gene**.

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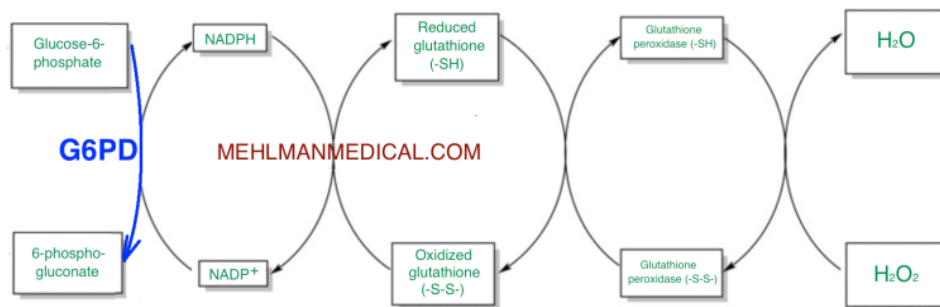
Now I'm going to briefly mention selenium and zinc.

How do they relate to vitamin A? They don't whatsoever. It's just that they HY points are short so I decided to not make a separate post for them.

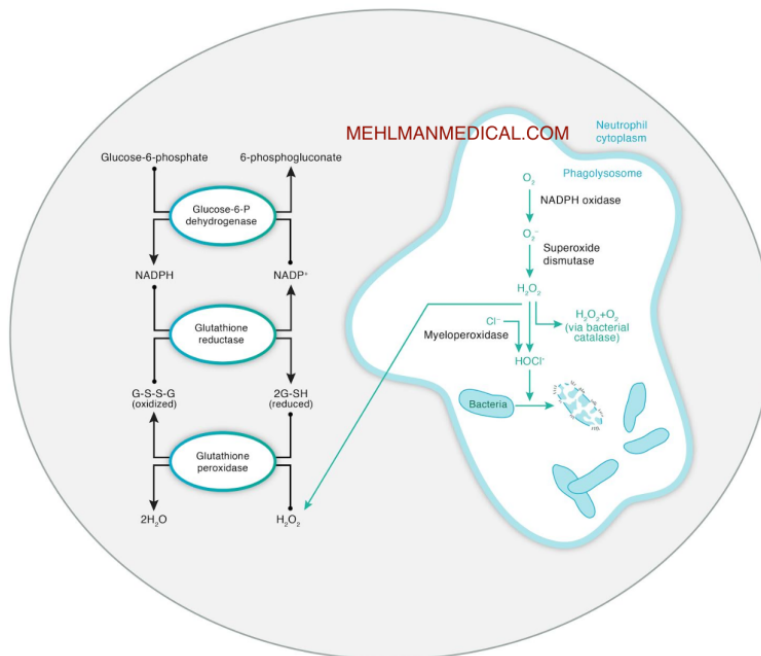
Selenium

All you need to know about selenium for Step1 is that it's a cofactor for **glutathione peroxidase**. That's it. And in case you don't recall, glutathione peroxidase converts $\text{H}_2\text{O}_2 + \text{reduced glutathione (-SH)} \rightarrow \text{H}_2\text{O} + \text{oxidized glutathione (-S-S-)}$.

This ultimately ties into **G6PD deficiency** because of how the reaction works together with glutathione reductase, which requires NADPH.



The hydrogen peroxide from this reaction is made in the **respiratory burst**:



Zinc

Roughly 80% of questions that ask about zinc deficiency on USMLE Step1 will present a patient with **anosmia** (↓ ability to smell) and **dysgeusia** (↓ ability to taste). These patients also have ↓ **wound healing**.

About 20% of the time you'll get a question on zinc deficiency that gives a patient with **acrodermatitis enteropathica**, an autosomal recessive condition characterized by ↓ zinc absorption, **dermatitis of orifices/limbs**, **diarrhea**, and **alopecia**.

Zinc deficiency has also been known to cause infertility.

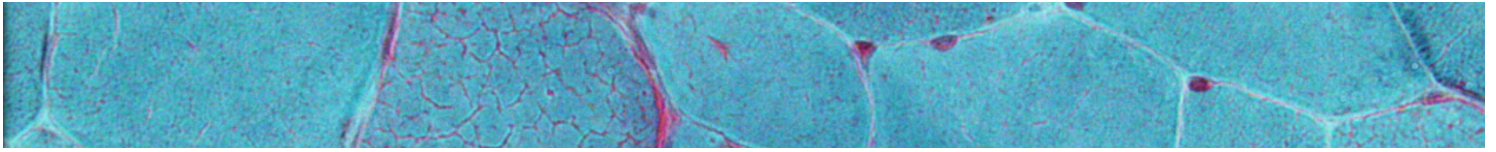
Just as fructose is secreted into semen by the seminal vesicles, the prostate secretes zinc into semen, which helps stabilize DNA-containing chromatin in spermatozoa.

1. What does vitamin A do in phototransduction?

- ☐ Helps convert 11-cis-retinal to 11-trans-retinal
- ☐ Helps convert 11-trans-retinal to 11-cis-retinal

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BIOCHEMISTRY

Vitamin B1 (Thiamine) + Wernicke-Korsakoff

by MEHLMANMEDICAL

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Thiamine-dependent enzymes

For starters, you must know the four thiamine (vitamin B1)-dependent enzymes:

- 1) **Pyruvate dehydrogenase** (pyruvate → acetyl-CoA)
- 2) **α-ketoglutarate dehydrogenase** (α-KG → succinyl-CoA in the [TCA cycle](#))
- 3) **Branched-chain amino acid dehydrogenase** (deficient in [MSUD](#))
- 4) **Transketolase** (produced in [HMP shunt](#))

An ↑ in RBC transketolase activity >15% following B1 administration means B1 deficiency was severe; <5% ↑ indicates thiamine was not deficient.

If you ever get a question where they mention transketolase in relation to thiamine, increased RBC transketolase activity following thiamine administration means the patient was thiamine-deficient.

There's no hard and fast rule, but you can remember thiamine is generally a cofactor for **dehydrogenase reactions**.

Thiamine deficiency

Most often seen in the setting of chronic alcoholism. The mechanism is simply **dietary deficiency**. Alcohol doesn't magically impede the absorption of thiamine.

Ethanol is 7 kcal/gram, so alcoholics tend to fill up on what they drink and don't consume much else, putting them at risk for B vitamin deficiencies.

Dry beriberi (neuropathy) → classically numbness of the hands + feet, but can present with an array of non-specific features, including confusion.

Wet beriberi (dilated cardiomyopathy) → lateralized apex beat, S3 heart sound, bilateral pulmonary infiltrates, increased pulmonary capillary wedge pressure (PCWP), cephalization of the pulmonary vessels (pulmonary edema).

Important point: Thiamine-deficiency and chronic alcoholism can **BOTH** cause dilated cardiomyopathy **THAT ARE DISTINCT FROM EACH OTHER**.

In other words, one of the causes of dilated cardiomyopathy is literally direct myocardial damage from chronic alcohol use, whereas a separate cause is thiamine deficiency. It is merely a coincidence that thiamine deficiency is seen in alcoholics.

Alcohol can also damage skeletal muscle, increasing the risk of **rhabdomyolysis**, as well as the bone marrow, leading to **non-megaloblastic macrocytic anemia**.

Wernicke encephalopathy is HY for B1 deficiency. There's a triad you need to remember:

A COW: Ataxia, Confusion and Ophthalmoplegia, Wernicke

That's the classic triad.

However if the USMLE asks you for what could occur by giving glucose to a patient without first giving thiamine, **anterograde amnesia** is sometimes the answer.

If you administer glucose to an unconscious patient or in the setting of suspected alcohol use:

Never give glucose without thiamine.

If the patient is thiamine-deficient, excess pyruvate produced through glycolysis will be shunted to additional lactate. Wernicke encephalopathy will also be acutely worsened, exacerbating the patient's confusion and anterograde amnesia.

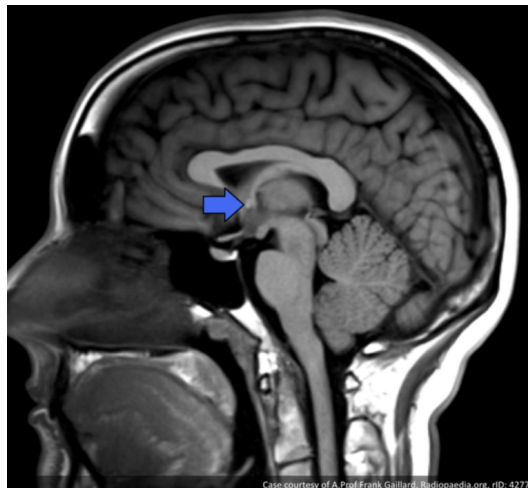
Korsakoff psychosis, which occurs in even more advanced disease, is associated with **retrograde amnesia + confabulations**.

Confabulations are made up statements about the past / what the patient was doing earlier in the day to compensate for lack of memory.

The combination of the two pathologies is simply referred to as Wernicke-Korsakoff (W-K) syndrome.

Extremely HY is knowing that the **mammillary bodies** are frequently damaged in W-K.

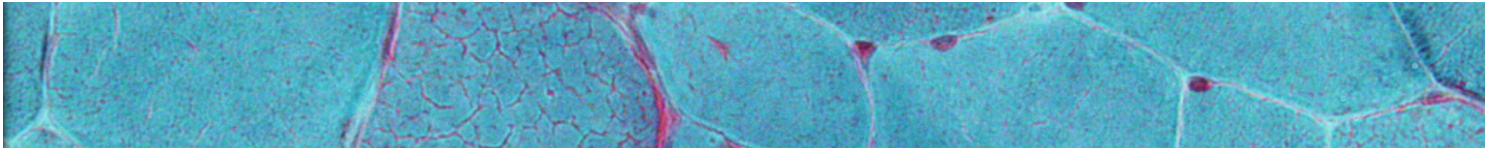
The **medial dorsal nucleus of the thalamus** is also thought to be damaged in W-K.



The USMLE will sometimes ask you to identify the **mammillary bodies** on MRI.

For more on alcohol withdrawal, including delirium tremens and alcoholic hallucinosis, as well as alcohol metabolism and effects, I talk about all of that stuff in [this post](#).

—
1. What are the four thiamine-dependent enzymes?



BIOCHEMISTRY

Vitamins B2 (Riboflavin) + B3 (Niacin)

by MEHLMANMEDICAL

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Riboflavin (vitamin B2)

Not a commonly tested vitamin on Step1, but mentioning it here for the sake of comprehensiveness prior to talking about niacin.

It's a cofactor for any reaction involving **FAD/FADH₂** or FMN. This means B2 is a cofactor for oxidation/reduction reactions.

Remember that FADH₂ is produced via **succinate dehydrogenase** in the conversion of **succinate** → **fumarate** in the **TCA cycle**.

Most students won't be able to identify the succinate → fumarate step of the TCA cycle as the one that relates to vitamin B2.

If you get a question assessing B2 deficiency (ariboflavinosis), the one thing you want to be on the lookout for is **corneal vascularization** combined with angular cheilosis. The latter is a common finding in B vitamin deficiencies in general, but the corneal vascularization is what they like for ariboflavinosis.

Now for the real stuff.

Vitamin B3 (niacin)

Do not walk into the Step1 testing center without knowing everything from this entry on niacin.

It is used in reactions involving **NADH/NAD⁺** or **NADPH/NADP⁺**. B6 and B2 are needed for its synthesis.

If used as a lipid-improving agent, it does two things:

- 1) It increases HDL.
- 2) It decreases hepatic export of VLDL (↓ TGAs)

It used to be that point #1 was emphasized in isolation, but the USMLE is now asking for point #2.

Side-effects of niacin

Although niacin increases HDL and decreases TGAs, we do not use it clinically because of its side-effects, in combination with lack of evidence for its clinical benefit, notably in patients already receiving statins for cardiovascular disease (New England Journal of Medicine article [here](#)).

Niacin (not even excess; just supplemental niacin in general, taken within the therapeutic range) can cause:

1) Flushing of the face and body

- Treated with aspirin
- This therefore means the flushing is due to **PROSTAGLANDINS**, **not histamine**.
- Think about it. Aspirin is the Tx, and inhibition of COX leads to ↓ prostaglandin synthesis.
- The USMLE loves asking this question. **Histamine is the #1 wrong answer**.

2) Hyperglycemia due to insulin resistance

- Pushes patients who are pre-diabetic into type-II diabetes
- Worsens type-II diabetes
- If the USMLE asks you how the dose of a T2DM patient's hypoglycemic med needs to be tweaked if taking niacin, the answer is **the dose must be increased**.

3) Gout due to hyperuricemia

- USMLE will tell you a guy has a history of podagra (swollen big toe from gout) and then ask you which drug is contraindicated in this patient. Answer is simply niacin.

Niacin deficiency is called **pellagra**. Do not confuse that with **podagra**, which is gout of the big toe.

Niacin deficiency

As discussed [here](#), the most commonly tested causes of niacin deficiency are:

- **Hartnup disease** (↓ tryptophan reabsorption in the kidney → ↓ niacin synthesis because tryptophan is the precursor).
- **Carcinoid syndrome** (tryptophan is the precursor of both niacin and serotonin. ↑ serotonin synthesis → depletion of tryptophan → ↓ niacin synthesis).

Pyridoxine (vitamin B6) deficiency secondary to isoniazid (INH) use for TB can also, in theory, cause B3 deficiency (B6 is a cofactor for the synthesis of niacin from tryptophan; INH for tuberculosis → ↓ B6). It's essentially a scenario where niacin deficiency doesn't actually happen this way in real life, but the USMLE can ask this in a "what could theoretically happen" type of question.

Deficiency of niacin causes **pellagra**. This presents as the "3Ds," = dementia, dermatitis, diarrhea.

It should be noted that one of the biggest risk factors for delirium is underlying dementia. That is, an elderly patient with decreased mental reserve is much more likely to experience delirium than a young, healthy patient. This means:

Rather than dementia, a pellagra vignette can present as an elderly, hospitalized patient with **delirium instead**. Then when you're like, "wait wtf?" If you realize that patients with underlying dementia are more easily able to get delirium, it makes sense.

73-year-old male in hospital has visual hallucinations, hyperpigmentation of his forearms, and increased bowel motions. Which vitamin is deficient?

B3.

Some resources will discuss the dermatitis in pellagra as classically presenting with Casal necklace (hyperpigmentation of sun-exposed neck), but bear in mind the forearms can easily be just as sun-exposed.

A general point about niacin

If a patient has low HDL, the best initial Tx is recommending lifestyle change.

However, the **most effective way** to increase HDL is **niacin**. That is, niacin exceeds lifestyle changes in efficacy of increasing HDL levels.

Patient has low HDL. Next best step in management to increase it?

Answer = **lifestyle modification** – i.e., smoking cessation, exercise, healthy diet, **1-2 alcoholic drinks per day** (yes, superior to zero; the UpToDate article is [here](#)).

Patient has low HDL. *Most effective way* to increase it?

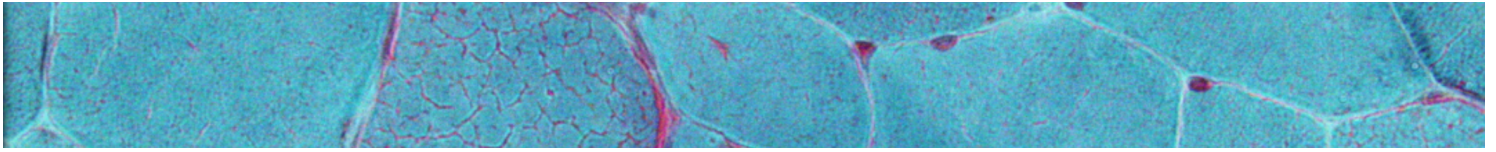
Answer = niacin. We don't actually prescribe niacin in real life because of its side-effects + it hasn't been proven to improve outcomes, but niacin is still most effective in increasing HDL.

—

1. What kinds of reactions is riboflavin (vitamin B2) used for?

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BIOCHEMISTRY

Vitamins B5, B6, and B7

by MEHLMANMEDICAL

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Vitamin B5 (pantothenic acid)

Probably the least commonly tested vitamin on Step1, but here's what you need to know:

- It is a coenzyme-A (CoA) reactions.
- Deficiency can cause **adrenal insufficiency** and **burning feet syndrome** (paresthesias/dysesthesias).

That's it. That's all you need to know about B5.

Vitamin B6 (pyridoxine)

Depleted with isoniazid (INH) use for TB.

- The highest yield thing on Step1 to know about vitamin B6 is that **isoniazid (INH) used for TB causes B6 deficiency**. Seizures or neuropathy in the setting of TB Tx always = B6 deficiency on Step1. Always give pyridoxine with INH. And the **USMLE will sometimes list "pyridoxine" instead of "vitamin B6"** as an answer choice.

Cystathionine synthase requires B6 as a cofactor.

- Vitamin B6 is adjunct therapy for homocysteinuria, since the formation of cystathionine requires B6 as a cofactor.
- For more on this, see my post on homocysteinuria [here](#).

Vitamin B6 is needed for heme synthesis.

- Deficiency of B6 leads to **sideroblastic anemia**.
- In the first step of heme synthesis, **succinyl-CoA + glycine → δ-aminolevulinic acid**, via vitamin B6.

B6 is needed for decarboxylase reactions.

- Histidine → **histamine**, via **histidine decarboxylase + B6**
- Glutamic acid → **GABA**, via **glutamic acid decarboxylase + B6**

Seizures caused by vitamin B6-deficiency secondary to INH use are due to **decreased GABA**.

B6 is needed for B3 synthesis.

- As discussed [here](#), B6 and B2 are needed for niacin biosynthesis.

B6 is used for hepatic transaminase reactions.

- Pyridoxine is also needed for transaminase reactions (i.e. **the liver enzymes ALT and AST**).
- Pyruvate + glutamate $\leftrightarrow$ α -KG + alanine (via ALT and B6)
- OAA + glutamate $\leftrightarrow$ α -KG + aspartate (via AST and B6)

Biotin

Required for carboxylase reactions.

- Acetyl-CoA $\rightarrow$ malonyl-CoA (via acetyl-CoA carboxylase + B7)
- Pyruvate $\rightarrow$ oxaloacetate (via pyruvate carboxylase + B7)
- Propionyl-CoA $\rightarrow$ methylmalonyl-CoA (via propionyl-CoA carboxylase + B7)
- I give a little more context on the latter two reactions [here](#).

Carboxylase reactions add CO₂ to a molecule; decarboxylase reactions remove CO₂.

Deficiency is caused by consumption of raw egg whites

- Most common cause of B7 deficiency is consumption of raw egg whites (old-fashioned organic body builders).
- The whites contain avidin, a B7-binding molecule.
- Yolks contain lots of B7, so only isolated, ongoing, raw egg white consumption $\rightarrow$ B7 deficiency.
- Cooking egg whites denatures avidin.

—

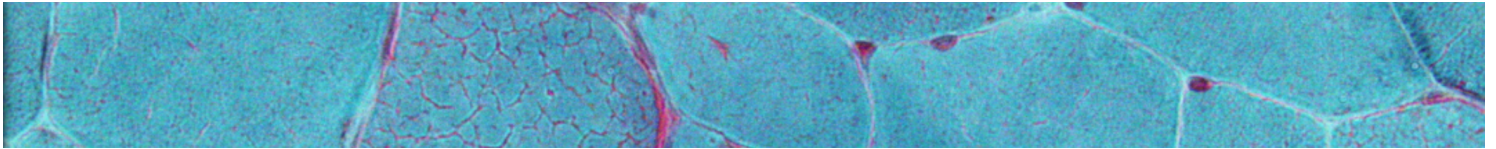
1. What kinds of reactions is vitamin B5 (pantothenic acid) used for? And what does deficiency cause (two things)?

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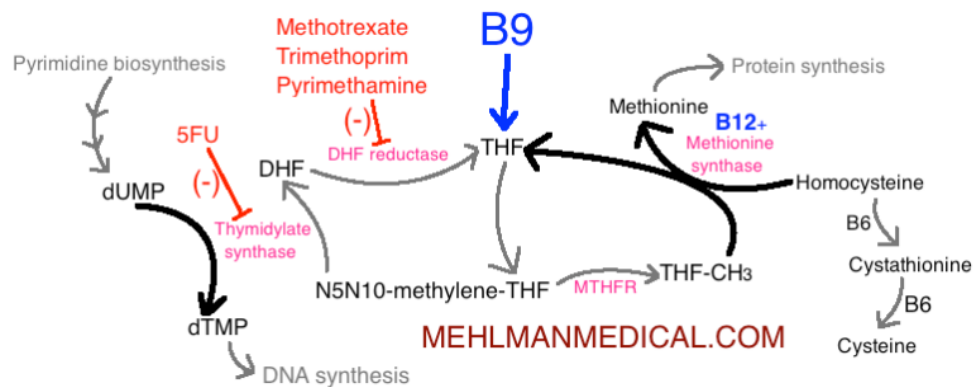
Vitamins B9 (Folate) + B12

by MEHLMANMEDICAL

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Dietary folate (B9) is converted to tetrahydrofolate (THF) for use in various reactions.

- Once in the form of THF, it can become THF-CH₃ or N⁵N¹⁰-methylene-THF.
- After conversion to THF-CH₃, vitamin B12 is a second cofactor that is used for methionine synthesis from homocysteine.
- After conversion to N⁵N¹⁰-methylene-THF, thymine can be made from uracil.

B9 is found in dark, green, leafy vegetables.

- If the USMLE asks you for the most likely nutrient deficiency in a vegan or strict vegetarian, but B12 is not listed, folate is the wrong answer. The correct answer is calcium, which is normally found in high amounts in fish and dairy.
- Folate deficiency is the most common vitamin deficiency in the United States.
- B12 is the only water-soluble vitamin that has a few years of stores before deficiency occurs. In contrast, folate stores deplete within ~6 months of low intake.
- If you get a USMLE vignette of an elderly woman on a tea and toast diet the past 6 months and her MCV is elevated, the answer is folate deficiency, not B12.

B9 or B12 deficiency causes megaloblastic anemia + hypersegmented neutrophils.

- Highest yield point to know for the USMLE regarding these vitamin deficiencies.
- Normal RBC MCV is 80-100 fL. Megaloblastic would be >100.
- Neutrophils normally have nuclei with 2-4 lobes. Hypersegmented ones have 5-7. If the USMLE is showing you one on an image it will be obvious.

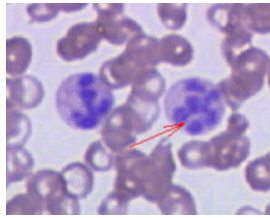


Image courtesy of Wikipedia.
Cheers mate.

Maternal deficiency of B9 in the first three pregnancy leads to neural tube defects.

- The neural tube forms at gestational weeks 3-4.
- Women planning for pregnancy should take 400 micrograms daily of folic acid. This should be continued throughout pregnancy as part of a standard pregnancy multivitamin, although it's just the first 3-4 weeks where adequate folate is paramount.
- USMLE wants you to know that **anti-epileptic meds** (i.e., phenytoin, **valproic acid**, and carbamazepine) can cause folate deficiency by impairing gut absorption.
- Women with Hx of pregnancy with fetal neural tube defects or Hx of taking anti-epileptic medications require 4 mg of folate daily (10x standard dose).

Folate deficiency is the most common vitamin deficiency.

- B12 is the only water-soluble vitamin that has a few years of stores before deficiency occurs. In contrast, folate stores deplete within ~6 months of low intake.

Vitamin B12 (cyanocobalamin) is involved in two key reactions on the USMLE.

- **Homocysteine** → **methionine**, via methionine synthase, for use in protein synthesis. (Homocystinuria post [here](#)).
- **Methylmalonyl-CoA** → **succinyl-CoA**, via methylmalonyl-CoA mutase. (Gluconeogenesis post [here](#)).

Blood levels of methylmalonyl-CoA and homocysteine

- **Both are increased in B12 deficiency; only homocysteine is increased in B9 deficiency.**
- This is because B12 is a cofactor for both homocysteine → methionine, and methylmalonyl-CoA → succinyl-CoA.
- In contrast, THF-CH₃ (derived from B9) is only needed for homocysteine → methionine.
- Since homocysteine is elevated in both B9 and B12 deficiencies, **increased serum methylmalonyl-CoA in the blood is a hallmark of B12 deficiency.**

Patient with ↑ MCV.

Serum methylmalonyl-CoA elevated? Yes, elevated → B12 deficiency

Serum methylmalonyl-CoA elevated? No, not elevated → B9 deficiency

(Homocysteine is ↑ in both)

Causes of B12 deficiency are exceedingly HY on the Step.

- **Pernicious anemia.** Autoantibodies against gastric parietal cells (or intrinsic factor) lead to impaired B12 absorption. Intrinsic factor binds to B12 so that it can be absorbed in the terminal ileum.
- **Veganism or strict vegetarianism.** B12 is found largely in meat and fish.
- **Surgery** (i.e., gastric bypass, or terminal ilectomy)
- ***Diphyllobothrium latum* infection.** It's a cestode (tapeworm).
- **Crohn disease**
- **Menetrier disease** (atrophy of parietal cells + mucous neck cell hyperplasia + enlarged stomach rugae that resemble brain gyri)
- Most B12 deficiency is due to malabsorption, rather than ↓ intake, which is why it is usually corrected parenterally.

If the USMLE tells you an, e.g., 22-year-old vegan with Hx of **autoimmune disease, e.g., autoimmune thyroiditis, vitiligo, etc.**, has $\uparrow$ MCV + hypersegmented neutrophils, they want **pernicious anemia as the most likely answer**, not dietary deficiency.

Autoimmune diseases "go together," meaning if you have one, you have increased risk for another. The HLA associations are not that strict.

B12 deficiency is a reversible cause of cognitive decline

- Any patient, particularly elderly, who has possible dementia, he or she needs evaluation for **depression** (pseudodementia), **hypothyroidism** (check TSH levels), and **B12 deficiency**.
- And clearly if a patient is vegan or strict vegetarian, any cognitive dysfunction should be evaluated within the context of checking B12 levels.

Subacute combined degeneration

- The name given to the pattern of neurologic dysfunction seen in B12 deficiency. Occasionally questions will simply list this disease name as an answer, so know it.
- Decreased ability to convert methylmalonyl-CoA $\rightarrow$ succinyl-CoA leads to buildup of methylmalonyl-CoA, which is **toxic to myelin**.
- You must know the three tracts that are involved. It is a triad of demyelination of the **lateral corticospinal tracts, spinocerebellar tracts and dorsal columns**.

I find an easy way to remember which three tracts are affected is to start by saying, "The spinothalamic tract is not involved."

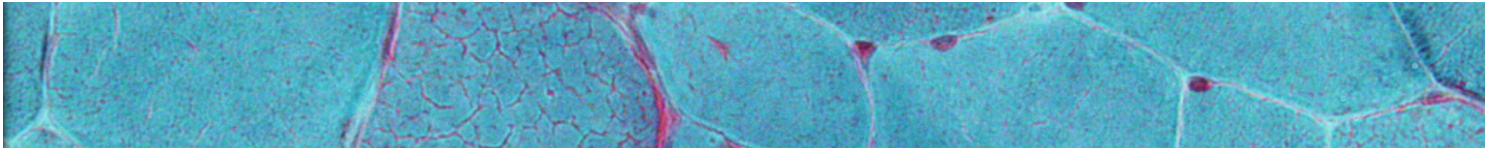
Schilling test

- Tests for etiology of B12 deficiency
- First give patient B12 injection to make sure he or she is replete.
- Then give radiolabeled oral B12.
- If radiolabeled B12 is seen in urine, the **cause of the deficiency is dietary**.
- If not seen in urine, next give radiolabeled B12 orally with intrinsic factor.
- If seen in urine, **cause is pernicious anemia**.
- If not seen in urine, **cause is intestinal** (e.g., Celiac, Crohn, infective, etc.).

1. Name three drugs that inhibit dihydrofolate reductase.

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BIOCHEMISTRY

Vitamins C and E

by MEHLMANMEDICAL

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Why did I group these together and skip over D? Because discussion of D is annoyingly lengthy and requires its own post.

Vitamin C (ascorbic acid / ascorbate)

Most important function on the USMLE is for collagen synthesis

- **Vitamin C is necessary for collagen synthesis.** More specifically, it is required for the hydroxylation of proline and lysine residues within procollagen.
- The hydroxylation allows for crosslinking between amino acid **secondary structure** (H-bonds) within the collagen, thereby strengthening it.
- **Scurvy (vitamin C deficiency)** results in weakened collagen and easy bleeding.

Subperiosteal and **perifollicular hemorrhages** are specific to scurvy.

Bleeding from gums and an **ill-appearing** patient are also frequent vignette descriptors.

Yes, “ill-appearing” sounds vague, but the USMLE will actually say that in question stems.

For scurvy, be on the lookout for metaphyseal thickening and fragmentation around the epiphyseal plates, corkscrew-shaped hair, multiple fractures, bruised/swollen joints, petechiae, and iron-deficiency anemia.

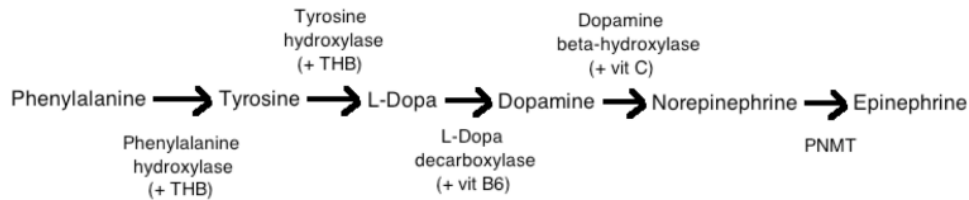
DO NOT confuse the presentation of scurvy with that of **Menkes syndrome**.

Scurvy presents with “corkscrew” hair, **but Menkes presents with “kinky” hair** and neurological/mental impairment. Ridiculous, but this is what the USMLE tests.

And only in scurvy will there be a mention of blood around hair follicles (perifollicular hemorrhages).

Required for catecholamine synthesis

- Catecholamine synthesis (i.e., dopamine, norepinephrine, epinephrine) is also dependent on vitamin C.
- This is because **dopamine β -hydroxylase**, which converts dopamine to norepinephrine, requires vitamin C.



Required for duodenal absorption of iron

- **Vitamin C ferriredutase**, which converts Fe^{3+} at the apical enterocyte membrane to Fe^{2+} . Only the Fe^{2+} state of iron can be absorbed.
- Therefore, vitamin C is necessary for iron absorption and deficiency can cause **iron deficiency anemia** (at least in theory on the USMLE).
- You'll often see combined vitamin C-iron supplements in pharmacies for this reason.

Hypervitaminosis C can cause calcium oxalate stones

- Just memorize it. Vitamin C toxicity can cause calcium oxalate nephro-/ureterolithiasis via ↓ pH of urine to favor crystal deposition.
- Patient taking high-dose multivitamin and gets shooting groin pain → CaOxalate stones from excess vitamin C. Mind-blowing.
- Toxicity can also cause **iron overload** (↑ absorption), at least in theory.

Vitamin E (tocopherol / tocotrienol)

Protects RBCs from hemolysis

- Vitamin E is an anti-oxidant that **protects RBCs from hemolysis**. In the event of vitamin E deficiency, **hemolytic anemia** can occur because of **increased RBC fragility**.

Hypervitaminosis E can cause bleeding diathesis

- Hypervitaminosis-E can lead to **increased INR**.
- It is hypothesized that vitamin E interferes with vitamin K function and can lead to bleeding diathesis in patients on warfarin.

Deficiency can cause neurologic dysfunction

- Vitamin B12 deficiency also causes neurologic dysfunction, but the vignette may also mention hemolysis, which is not seen in B12 deficiency.
- A point of distinction between B12 and E deficiencies is that the former results in **subacute combined degeneration**, where the **dorsal columns, spinocerebellar tracts, and corticospinal tracts** are affected. This exact pattern is not seen in vitamin E deficiency.

Vitamin deficiency + neurologic dysfunction:

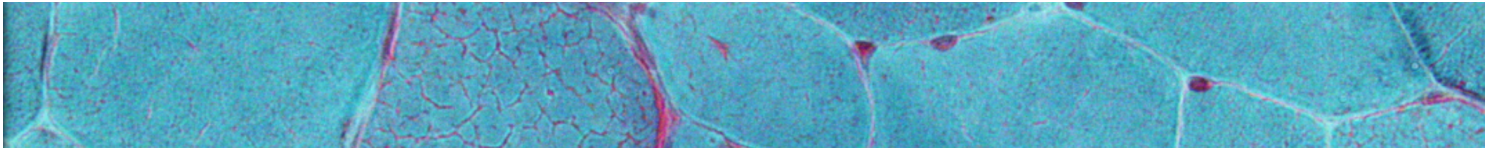
↑ MCV + ↑ serum methylmalonyl-CoA = B12 deficiency

Hemolysis (↑ unconjugated bilirubin) + **normal** serum methylmalonyl-CoA = vitamin E deficiency

1. a) Iron is absorbed where?

b) And in what ionic state?

c) How does this relate to a vitamin?



BIOCHEMISTRY

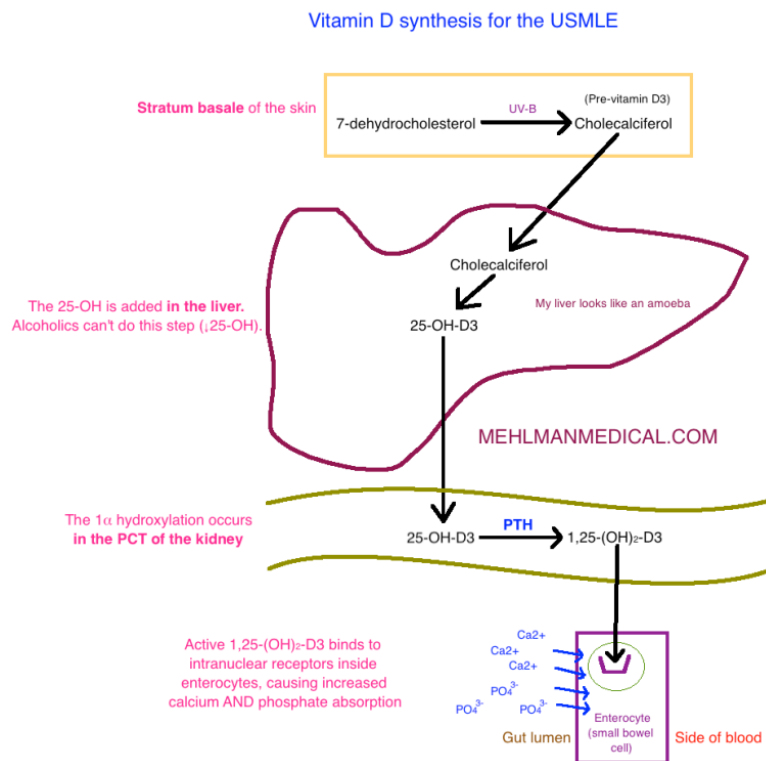
Vitamin D for the USMLE

by MEHLMANMEDICAL

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The USMLE is pedantic about how/where in the skin this occurs.

- Vitamin D synthesis is initiated in the **stratum basale / basal layer**. This specific detail regarding *where* in the skin is currently being tested on USMLE Step1.
- In the skin, 7-dehydrocholesterol, via UV-B, → cholecalciferol.
- A person who is vitamin D deficient from decreased sun exposure will have ↓ **cholecalciferol**. There will be **normal** levels of 7-dehydrocholesterol.

The 25-OH hydroxylation step occurs in the liver.

- Cholecalciferol → 25-hydroxyD3 (calcidiol) **in the liver**.

- 25-hydroxyD3 is an inactive form.
- If they give you an alcoholic who has vitamin D deficiency, select **decreased hepatic hydroxylation** as the answer.
- Students frequently get this question wrong because USMLE resources tend to overly fixate on the 1α hydroxylation that occurs in the kidney.

Parathyroid hormone (PTH) induces the 1α (activating) hydroxylation in the PCT of the kidney

- PTH induces the conversion of 25-hydroxyD3 $\rightarrow$ $1,25\text{-(OH)}_2\text{-D3}$ (calcitriol) in the **PCT of the kidney**.
- $1,25\text{-(OH)}_2\text{-D3}$ is the active form of vitamin D3.
- Hypoparathyroidism causes $\downarrow$ in 25-OH-D3 and $\downarrow$ $1,25\text{-(OH)}_2\text{-D3}$.

$1,25\text{-(OH)}_2\text{-D3}$ causes increased calcium AND phosphate absorption in the small bowel

- BOTH are absorbed more in the small bowel secondary to the effects of vitamin D.
- Vitamin D deficiency therefore causes $\downarrow$ **calcium AND** $\downarrow$ **phosphate** in the serum.
- $1,25\text{-(OH)}_2\text{-D3}$ also increases bone **resorption**.

USMLE wants you to know your arrows for rickets / osteomalacia

The USMLE likes to turn vitamin D deficiency into an arrow-type question. You need to know:

$\downarrow \text{Ca}^{2+}$ | $\downarrow \text{PO}_4^{3-}$ | $\uparrow \text{ALP}$ | $\uparrow \text{PTH}$

ALP levels reflect $\uparrow$ osteoblastic activity. PTH binds to and activates osteoblasts (which causes them to express RANK-L in order to activate osteoclasts to break down bone).

In rickets/osteomalacia, there is a rise in PTH to compensate for the low Ca^{2+} , so ALP is up. Even if not all patients have $\uparrow$ ALP and PTH in real life, this is how the USMLE tests it.

The rickets / osteomalacia pathologic descriptions are exceedingly HY

- For rickets, classic signs are **Harrison sulci** (indentations of lower ribs), **craniotabes** (softening of the skull), and **rachitic rosary** (bony prominences at the costochondral junctions).
- The USMLE might describe rickets as a child with **widened wrists/ankles and marked enlargement of the costochondral junctions**.
- **Bowing of the tibiae (genu varum)** is a HY finding in rickets.
- They also want you to know that whereas bone in osteoporosis has a porous, hollowed-out structure, in rickets/osteomalacia, there is **disordered bone with $\uparrow$ osteoid**.
- Osteoid is unmineralized bone.
- Without vitamin D, but the bone cannot mineralize the osteoid because calcium and phosphate levels are insufficient.
- **Pseudofractures** = a key word / x-ray finding seen in vitamin D deficiency. Just memorize it.

A 6-year-old boy has genu varum. Calcium, phosphate, ALP, PTH levels?

$\downarrow \text{Ca}^{2+}$ | $\downarrow \text{PO}_4^{3-}$ | $\uparrow \text{ALP}$ | $\uparrow \text{PTH}$

Chronic renal failure presents a rare exception regarding phosphate

- In **chronic renal failure**, vitamin D activation via 1α hydroxylation in the PCT may be impaired, leading to $\downarrow$ $1,25\text{-(OH)}_2\text{-D3}$.
- So you might think, "Well, if we have vitamin D deficiency, then calcium and phosphate are both down."
- But in renal failure, **phosphate is always up no matter what** because the kidney can't filter + secrete it out.
- In other words, despite the vitamin D deficiency, **phosphate will be up in renal failure**.
- But for vitamin D deficiency in the absence of renal failure, both calcium and phosphate are down.
- In short, **renal failure wins when it comes to arrows. Always select high phosphate in renal failure**.

A long-standing diabetic with renal failure has hip pain. X-ray shows a pseudofracture of the femoral head. Calcium and phosphate levels?

Calcium is down; phosphate is UP.

Hypervitaminosis D is due to granulomatous disease

- High vitamin D levels are not because some girl went to the pharmacy and decided to OD on vitamin D pills. High vitamin D levels are almost always due to **sarcoidosis** on the USMLE.
- The non-caseating granulomas in the lungs, kidney, etc., in sarcoidosis have epithelioid macrophages that secrete 1α hydroxylase. This increases the active form of vitamin D ($1,25-(OH)_2-D_3$) and leads to hypercalcemia +/- hyperphosphatemia.
- Classic hypervitaminosis D presents with high calcium and phosphate, but I've seen an occasional question where phosphate is normal. That's just a heads up so you're not dumbfounded if/when you encounter that.
- However if you get an arrow question and are forced to choose, always select $\uparrow$ **calcium AND** $\uparrow$ **phosphate**.

Effects of high vs low calcium due to vitamin D levels

- Any time there is vitamin D deficiency and $\downarrow$ serum Ca^{2+} , there is the possibility of **hypocalcemic tetany**.
- In contrast, hypervitaminosis D is associated with hypercalcemia and **flaccidity**.

$24,25-(OH)_2-D_3$ is a storage form of D_3 and is asked in a key, HY way

- If a patient has hypoparathyroidism ($\downarrow$ PTH), there will be $\downarrow$ $1,25-(OH)_2-D_3$ and $\uparrow$ in $25-OH-D_3$.
- However, $25-OH-D_3$ is rapidly converted to a storage form called $24,25-(OH)_2-D_3$.
- For all intents and purposes, memorize $24,25-(OH)_2-D_3$ as being synonymous with $25-OH-D_3$ if you are confronted with an arrow question.

Miscellaneous

- **Breast milk has low vitamin D.** If a mother is exclusively breastfeeding and asks about a vitamin that could be optionally supplemented for her child, vitamin D is the answer.
- **William syndrome** is condition characterized by hypercalcemia 2° to $\uparrow$ vitamin D sensitivity. It is AD and on chromosome 7. There are well-developed verbal skills and elfin-like facies. They can be born with **supravalvular aortic stenosis**. Not a HY condition but shows up once in a blue moon.
- **Calcipotriene** is a topical vitamin D used in the Tx of plaque psoriasis.

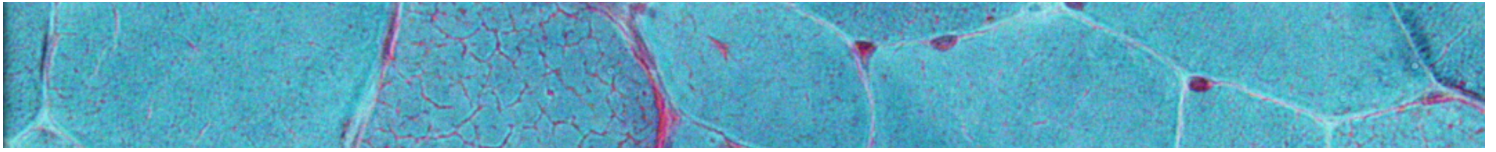
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1. Where in the skin does vitamin D synthesis start?

- ☐ Stratum corneum
- ☐ Stratum lucidum
- ☐ Stratum granulosum
- ☐ Stratum spinosum
- ☐ Stratum basale
- ☐ Papillary dermis
- ☐ Reticular dermis
- ☐ Hypodermis

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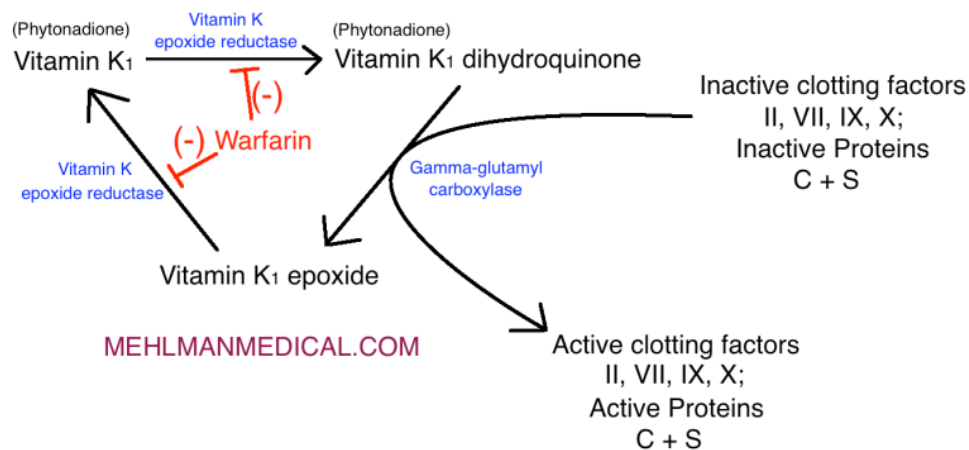
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Vitamin K and Warfarin

by MEHLMANMEDICAL



Vitamin K epoxide reductase

- Enzyme that recycles vitamin K₁ (phytonadione) so that it can be used for the gamma-carboxylation and activation of clotting factors.
- Warfarin inhibits this enzyme.
- In other words, warfarin inhibits the recycling of vitamin K₁ to its active form.
- Warfarin is often erroneously described as a "vitamin K antagonist." In reality, warfarin doesn't bind to and inhibit vitamin K directly, so this description is not accurate. Warfarin merely prevents the recycling of vitamin K to its active form, thereby antagonizing its effects indirectly.

Gamma-glutamyl carboxylase

- Vitamin K₁ is a cofactor for γ-glutamyl carboxylase.
- This is the enzyme that γ-carboxylates and activates clotting factors II, VII, IX and X, as well as anti-clotting proteins C & S.
- It γ-carboxylates **glutamic acid** residues on these factors.
- Vitamin K does not enable the hepatic synthesis of these factors; it merely *activates* them.

If you are asked which enzyme has ↓ activity in vitamin K deficiency, the answer is **γ-glutamyl carboxylase**.

If you are asked which enzyme has ↓ activity with warfarin use, the answer is **vitamin K epoxide reductase**.

Why prothrombin time (PT) is used to monitor warfarin's effects on vitamin K

- Warfarin is monitored with PT because Factor VII has the shortest half-life (4-7 hours) of the clotting factors, so **PT will prolong before aPTT does**.

- This means warfarin will prolong the extrinsic pathway (monitored with PT) before it prolongs the intrinsic pathway (monitored with aPTT).
- So if we want to accurately ascertain the effect or dose of warfarin in a patient, we need to look at the extrinsic pathway via PT because **it will tell us first** this information.

Vitamin K deficiency AND warfarin = ↑ PT and ↑ aPTT

- This is exceedingly HY.
- Because PT is used to monitor warfarin, people often assume warfarin ↑ PT and that's it. **But warfarin also ↑ aPTT.**
- Vitamin K deficiency is most often seen in newborns because of their sterile bowels. However it can also be due to **chronic antibiotic use** causing disruption of colonic normal flora.

Factor VII = extrinsic pathway only (PT)

Factor IX = intrinsic pathway only (aPTT)

Factors II, X = **common pathway (PT and aPTT)** → This explains why vitamin K deficiency and warfarin prolong both PT and aPTT.

Protein C inactivates Va and VIIIa (active forms) to V and VIII (inactive forms).

Protein S is a cofactor for Protein C.

International normalized ratio (INR)

- INR tells us how long our PT is compared to the expected range in the normal population.
- PT is normally 10-15 seconds. This means if an individual's PT is, e.g., 14 seconds, his or her INR is 1.0.
- We aim for a therapeutic effect of warfarin on the order of INR 2-3.
- So a patient on warfarin would be expected to have a PT of 20-45 seconds in theory.

Warfarin is broken down predominantly by CYP-2C9

- This factoid is so HY it needs its own heading.
- We normally hear about CYP-3A4 in passing. Most drugs are metabolized by this CYP. But warfarin is -2C9.

The USMLE is known to literally ask for which CYP is used for drug metabolism.

Most drugs are CYP-3A4.

Warfarin is CYP-2C9.

The microsomal ethanol oxidizing system (MEOS) is CYP-2E1.

P-450 inhibitors can cause bleeding diathesis

- Ciprofloxacin (a fluoroquinolone), macrolides, sulfa drugs, and metronidazole are particularly known to cause bleeding diathesis in patients on warfarin.

Skin necrosis is an adverse effect of warfarin in those who have hereditary Protein C deficiency

- If you get a question on why a patient may have experienced warfarin-induced skin necrosis, the answer is **Protein C deficiency**.
- The anti-clotting Protein C has a short half-life of 8 hours, meaning it will deplete with warfarin use long before II, IX, and X do.
- This means warfarin causes a transient hypercoagulable state (which is why it must be first bridged with heparin).
- Patients who are deficient in Protein C are therefore even more hypercoagulable, leading to greater risk of clotting in cutaneous microvasculature.

Treatment for vitamin K deficiency + the reversal of warfarin

- If the need to reverse warfarin occurs, if the scenario is not emergent (i.e., there is **NO** active bleeding or the patient doesn't require emergency surgery), **vitamin K is merely given**.
- If there **IS** active bleeding or the patient requires emergency surgery, the answer is **fresh frozen plasma (FFP) first, THEN vitamin K**.
- This is because vitamin K-mediated activation of clotting factors takes hours to days, whereas FFP works immediately, so giving vitamin K in emergency situations is futile to quickly reverse warfarin.

USMLE wants you to know vitamin K deficiency can occur in patients who are on chronic broad-spectrum antibiotics. They'll say patient on Abx is requiring a lower dose of warfarin to achieve same INR target range – why? → decrease in colonic normal flora.

Sources of vitamin K

- Exogenously through cruciferous vegetables (i.e., broccoli, Brussels sprouts, cabbage, cauliflower, kale, etc.).
- Endogenously through synthesis by gut flora.
- On the USMLE, if they ever ask you where we get most of our vitamin K from, the answer is always **via synthesis by colonic normal flora**.
- That is, if “green, leafy vegetables” and “colonic normal flora” are both answer choices, **the latter is always correct**.
- “Green, leafy vegetables,” in contrast, is always the answer for **folate**.

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1. What is the medical term for Vitamin K₁?

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